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PART II:

DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE

Food and Drug Administration

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OVER-THE-COUNTER DRUGS

Establishment of a Monograph for OTC Cold, Cough, Allergy, Bronchodilator and Antiasthmatic Products

DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE

Food and Drug Administration

[21 CFR Part 341]

[Docket No. 76N-0052]

OVER-THE-COUNTER DRUGS

Establishment of a Monograph for OTC Cold, Cough, Allergy, Bronchodilator and Antiasthmatic Products

The Food and Drug Administration (FDA) proposes to establish conditions under which over-the-counter (OTC) cold, cough, allergy, bronchodilator and antiasthmatic drugs are generally recognized as safe and effective and not misbranded, based on the recommendations of the Advisory Review Panel on Over-the-Counter (OTC) Cold, Cough, Allergy, Bronchodilator and Antiasthmatic Products; comments by December 8, 1976.

Pursuant to Part 330 (21 CFR Part 330), the Commissioner of Food and Drugs received on March 3, 1976, the report of the Advisory Review Panel on Over-The-Counter (OTC) Cold, Cough, Allergy, Bronchodilator and Antiasthmatic Products. In accordance with § 330.10(a)(6) (21 CFR 330.10(a)(6)), the Commissioner is issuing (1) a proposed regulation containing the monograph recommended by the Panel establishing conditions under which OTC cold, cough, allergy, bronchodilator and antiasthmatic drugs are generally recognized as safe and effective and not misbranded; (2) a statement of the conditions excluded from the monograph on the basis of a determination by the Panel that they would result in the drugs not being generally recognized as safe and effective or would result in misbranding; (3) a statement of the conditions excluded from the monograph on the basis of a determination by the Panel that the available data are insufficient to classify such conditions under either (1) or (2) above; and (4) the conclusions and recommendations of the Panel to the Commissioner. The summary minutes of the Panel meetings are on public display in the office of the Hearing Clerk, Food and Drug Administration, Rm. 4-65, 5600 Fishers Lane, Rockville, MD 20852.

The purpose of issuing the unaltered conclusions and recommendations of the Panel is to stimulate discussion, evaluation, and comment on the full sweep of the Panel's deliberations. The Commissioner has not yet fully evaluated the report, but has concluded that it should first be issued as a formal proposal to obtain full public comment before any decision is made on the recommendations of the Panel. The report of the Panel represents the best scientific judgment of the members. The report has been prepared independently of FDA and does not necessarily reflect the agency position on any particular matter contained therein. After a careful review of all comments submitted in response to this proposal, the Commissioner will issue a tentative final regulation in the FEDERAL REGISTER to establish a monograph for OTC cold, cough, allergy, bronchodilator and antiasthmatic drug products.

In accordance with § 330.10(a)(2) (21 CFR 330.10(a)(2)), all data and information concerning OTC cold, cough, allergy, bronchodilator and antiasthmatic drug products submitted for consideration by the Advisory Review Panel have been handled as confidential by the Panel and FDA. All such data and information shall be put on public display at the office of the Hearing Clerk, Food and Drug Administration, on or before October 12, 1976, except to the extent that the person submitting it demonstrates that it still falls within the confideniality provisions of 18 U.S.C. 1905 or section 301(j) of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 331(j)). Requests for confidentiality shall be submitted to FDA, Bureau of Drugs, Division of OTC Drug Products Evaluation (HFD-510), 5600 Fishers Lane, Rockville, MD 20852.

Based upon the conclusions and recommendations of the Panel, the Commissioner proposes, upon publication of the final regulation:

1. That the conditions included in the monograph on the basis of the Panel's determination that they are generally recognized as safe and effective and are not misbranded (Category I) be effective 30 days after the date of publication of the final monograph in the FEDERAL REGISTER.

2. That the conditions excluded from the monograph on the basis of the Panel's determination that they would result in the drug not being generally recognized as safe and effective or would result in misbranding (Category II) be eliminated from OTC drug products effective 6 months after the date of publication of the final monograph in the FEDERAL REGISTER, regardless whether further testing is undertaken to justify their future use.

3. That the conditions excluded from the monograph on the basis of the Panel's determination that the available data are insufficient (Category III) to classify such conditions either as Category I—generally recognized as safe and effective and not misbranded, or as Category II—not being generally recognized as safe and effective or would result in misbranding, be permitted to remain in use for not longer than 2 to 5 years (for the specific conditions specified in this document) after the date of publication of the final monograph in the FEDERAL REGISTER, if the manufacturer or distributor of any such drug utilizing such conditions in the interim conducts tests and studies adequate and appropriate to satisfy the questions raised with respect to the particular condition by the Panel. The period of time within which studies must be completed will be carefully reviewed by the Commissioner after receipt of comments on this document and will probably be revised downward.

This proposal sets forth the conclusion of the Advisory Review Panel on Over-the-Counter (OTC) Cold, Cough, Allergy, Bronchodilator and Antiasthmatic Products that several ingredients are safe and effective for OTC use which heretofore have been limited to prescription use or classified for OTC use at a dosage level lower than that recommended by the Panel. The Commissioner is aware that a number of questions have been presented to the agency regarding the OTC marketing status of ingredients or amounts of ingredients previously limited to prescription use prior to finalization of an applicable monograph for the ingredients. The reclassification of ingredients from prescription to OTC status presents important issues that need careful and special consideration.

Accordingly, the Commissioner proposed, in the FEDERAL REGISTER of December 4, 1975 (40 FR 56675), a policy to clarify the marketing status of (1) all ingredients currently restricted to prescription use which an OTC advisory panel recommends as Category I (safe and effective), Category II (not safe and effective), or Category III (the available data are insufficient to classify the drug); and (2) the use of active ingredients at dosage levels higher than that available in any OTC drug product.

The Commissioner also advised in the preamble to the proposal in the December 4, 1975 FEDERAL REGISTER that he may indicate his disagreement with the panel's recommendation(s) regarding specific ingredients proposed for Category I, e.g., ingredients having manufacturing or formulation problems or unresolved questions concerning a potential for abuse or misuse; and he may make a tentative determination that an approved new drug application (NDA) is required for marketing an OTC product containing such ingredients. The Commissioner acted on this proposal by final regulation published in the FEDERAL REGISTER of August 4, 1976 (41 FR 32580).

The Commissioner has reviewed those ingredients included in the Panel's recommendations that are currently limited to prescription use or classified for OTC use at a dosage level lower than that recommended by the Panel. He has made an initial determination that an approved NDA is required for OTC marketing of promethazine for any indication, for OTC marketing of doxylamine succinate as an antihistamine at a dosage level in excess of 7.5 milligrams (mg), and for OTC marketing of diphenhydramine as an antihistamine. The Commissioner is deferring his decision on the Panel's recommendation that diphenhydramine be considered generally recognized as safe and effective for OTC use as an antitussive until the agency has had an opportunity to rule on a supplemental NDA now pending for OTC use of an antitussive product containing diphenhydramine. The Commissioner has made an initial determination to accept the Panel's recommendations on OTC use of a number of ingredients among which are chlorpheniramine, pseudoephedrine, theophylline, and methoxyphenamine. However, the Commissioner wishes to raise several pertinent points regarding these drugs, and they are fully explained below.

Promethazine. The Panel recommended classification of the ingredient promethazine as a Category I OTC antihistaminic drug. This ingredient is presently a component of drug products that are the subject of approved NDA's for prescription use as antihistamines, as

sedatives, as antiemetics, as adjuncts with narcotics for preoperative sedation, and in the postoperative management of pain. Promethazine is the only antihistaminic drug reviewed by the Panel that is chemically identified as a phenothiazine derivative; no ingredients in this class are currently available for OTC use. Promethazine, like other phenothiazines, is known to produce certain serious adverse effects, including agranulocytosis, thrombocytopenia, hypoplastic anemia, extrapyramidal symptoms, and hypotension (*AMA Drug Evaluations*, 2d Ed., p. 497), although it may produce these less frequently than do other phenothiazines. Although these adverse effects are of considerable concern, the major consideration relates to the effects of promethazine on the central nervous system (CNS). Promethazine is known to have a hypnotic effect more conspicuous than that of the other antihistaminics (see Krantz and Carr, *The Pharmacologic Principles of Medical Practice*, 8th Ed., p. 818), a problem sufficient to cause the Panel to recommend a warning, "may cause marked drowsiness," a warning not required for OTC antihistamines in general. Overdosage is thus potentially a problem with promethazine, especially for children. Children also seem particularly liable to develop such CNS adverse reactions as disturbances of the psyche, changes in sensorium, evidence of extrapyramidal disturbances, convulsions, and, rarely, coma and death. The Commissioner notes that other OTC antihistamines are available that are as effective as promethazine and less hazardous. Thus the risk of adverse effects from OTC availability of this ingredient is not justified in the absence of an offsetting benefit in the form of therapeutic superiority in comparison with antihistamine ingredients already marketed OTC.

Doxylamine succinate. The Panel recommended classification of the ingredient doxylamine succinate as a Category I OTC antihistaminic drug at the 7.5 to 12.5 mg dosage level. This ingredient is presently the subject of an approved NDA for prescription use, and for OTC use at the 7.5 mg dosage level, for several indications, including the management of perennial and seasonal rhinitis and vasomotor rhinitis pursuant to the requirements of § 310.201(a)(13) (21 CFR 310.201(a)(13)). The Commissioner concludes that doxylamine succinate should continue to be classified as a new drug and a prescription drug at dosage levels in excess of 7.5 mg. The Commissioner makes this determination because other OTC antihistaminic agents are available that are safer than doxylamine succinate at that dosage level.

Doxylamine succinate is a member of the ethanolamine class of antihistamines. As noted in the *AMA Drug Evaluations*, 2d Ed., p. 493, this class of drugs exhibits a high incidence of drowsiness compared with the other classes of antihistamines (ethylenediamines and alkylamines). As noted in the proposal regarding OTC sleep-aid drug products, published in the FEDERAL REGISTER of December 8, 1975 (40 FR 57292), about 50 percent of those persons receiving conventional antihistamine treatment doses of drugs in the ethanolamine class experienced drowsiness. In addition to the pronounced tendency to induce sedation, drugs in this group also possess significant atropine-like activity. Therefore, the Commissioner concludes that doxylamine succinate should remain a prescription new drug ingredient at the dosage levels greater than 7.5 mg.

Diphenhydramine hydrochloride. Diphenhydramine hydrochloride is the active ingredient in several products with approved NDA's. All such products are limited to prescription use. The Panel recommended that diphenhydramine hydrochloride be classified in Category I for antihistaminic use at 25 to 50 mg, which is the usual prescription dosage level. Diphenhydramine hydrochloride, like doxylamine succinate, is a member of the ethanolamine class of antihistamines. It, too, has a pronounced tendency to produce sedation in a high proportion of those persons who take it (*AMA Drug Evaluations*, 2d Ed., p. 493). For this reason, the Commissioner concludes that diphenhydramine hydrochloride should remain a prescription new drug ingredient and not be available for use as an OTC antihistamine. No diphenhydramine hydrochloride product is currently marketed OTC as an antihistamine at any dosage level.

The Panel also recommended that diphenhydramine hydrochloride be classified in Category I for OTC use as an antitussive. Diphenhydramine hydrochloride is the active ingredient in a cough syrup product now being marketed OTC. The currently effective NDA for this product limits it to prescription use and labels it as an expectorant only. The holder of the NDA has submitted a supplemental NDA that contains data in support of a claim that the product is safe and effective for use as an antitussive. The supplemental NDA also requests that the product be approved for OTC use. The Commissioner has concluded that the marketing status of diphenhydramine hydrochloride as an antitussive should be resolved by first considering the approvability of this supplemental NDA. After that, he will address the Panel's recommendation that diphenhydramine hydrochloride be considered generally recognized as safe and effective for OTC use as an antitussive.

The agency will rule on the pending supplemental NDA in the near future. The Commissioner advises that if the supplemental NDA is denied because diphenhydramine hydrochloride in the amount present in that product is not considered safe and effective for OTC use as an antitussive, he will at that time issue a notice in the FEDERAL REGISTER stating his disagreement with the Panel's recommendation that diphenhydramine hydrochloride be classified in Category I for OTC antitussive use. In that event, any such product marketed OTC would thereupon be subject to immediate regulatory action, in accordance with the enforcement policy announced in the FEDERAL REGISTER of August 4, 1976 (41 FR 32580). If the supplemental NDA is approved, the Commissioner may nevertheless conclude that the safety and/or effectiveness of antitussive products containing diphenhydramine hydrochloride has not achieved general recognition in the scientific community, and he may state such conclusion by notice in the FEDERAL REGISTER when the supplemental NDA is approved or at a later time, e.g., in the preamble to the tentative final monograph.

The Commissioner notes that the marketing status of diphenhydramine hydrochloride as an antihistamine raises different issues from those surrounding its OTC use as an antitussive. The indications, dosage levels, and number of available effective alternatives are different depending on the condition for which diphenhydramine hydrochloride is to be used. Also, the effectiveness of the ingredient is established in relation to antihistaminic use, but has not yet been ruled on in the context of the pending supplemental NDA for OTC use of a cough syrup product. Accordingly, the Commissioner's initial decision not to accept the Panel's recommendation for Category I classification of diphenhydramine hydrochloride for use as an antihistamine is independent of his decision on its status as an antitussive, although, obviously, some of the underlying factual considerations are common to each.

Chlorpheniramine, pseudoephedrine, theophylline, and methoxyphenamine. The Panel recommended that chlorpheniramine as an OTC antihistamine and pseudoephedrine as an OTC oral nasal decongestant be available at dosage levels twice those currently permitted for OTC use. Although he does not disagree with these recommendations at this time, the Commissioner is concerned that consumers accustomed to purchasing a particular product may not be aware of the increased amount of active ingredient per dosage unit. The Commissioner concludes that consumers should be fully informed about the increased dosage. He has determined, therefore, that all manufacturers who elect to reformulate their marketed products shall clearly indicate any increased dosage level on the principal display panel of each product. He further suggests that, in the case of tablet formulations, scored tablets be available to assist the consumer in achieving a lower dosage, if one is desired.

The Panel further recommended that theophylline and methoxyphenamine be made available OTC as single ingredients. The Commissioner does not contest the judgment of the Panel regarding the safety of these ingredients. However, he points out that he believes there is a scientific issue whether the recommended dosage levels are therapeutically effective for a significant identifiable population of asthmatics. Therefore, these two ingredients are currently undergoing extensive review within the agency. Consequently, the decision of the Panel may be subject to modification in the tentative final monograph.

The Commissioner invites full public comment on all of the conclusions and

recommendations of the Panel, and on his own specific conclusions regarding promethazine, doxylamine succinate, diphenhydramine, chlorpheniramine, pseudoephedrine, theophylline, and methoxyphenamine.

The Commissioner has reviewed the potential environmental impact of the recommendations and proposed monograph of the Advisory Review Panel on OTC Cold, Cough, Allergy, Bronchodilator and Antiasthmatic Products and has concluded that the Panel's recommendations and proposed monograph will not significantly affect the quality of the human environment and that an environmental impact statement is not required. The Commissioner has also considered the inflation impact of the Panel's recommendations and proposed monograph, and no major inflation impact has been found, as defined in Executive Order 11821, OMB Circular A-107, and the Guidelines issued by the Department of Health, Education, and Welfare. Copies of the environmental and inflation impact assessments are on file with the office of the Hearing Clerk, Food and Drug Administration, Rm. 4–65, 5600 Fishers Lane, Rockville, MD 20852.

The conclusions and recommendations in the report of the Advisory Review Panel on OTC Cold, Cough, Allergy, Bronchodilator and Antiasthmatic Products follow:

In the FEDERAL REGISTER of January 5, 1972 (37 FR 85), the Commissioner of Food and Drugs announced a proposed review of the safety, effectiveness and labeling of all OTC drugs by independent advisory review panels. On May 8, 1972, the Commissioner signed the final regulations providing for the OTC drug review under § 330.10 published in the FEDERAL REGISTER of May 11, 1972 (37 FR 9464), which were made effective immediately. Pursuant to these regulations the Commissioner issued a request for data and information on all cold, cough, allergy, bronchodilator and antiasthmatic (CCABA) active ingredients in drug products, in the FEDERAL REGISTER of August 9, 1972 (37 FR 16029).

The Commissioner appointed the following Panel to review the data and information submitted and to prepare a report on the safety, effectiveness, and labeling of OTC cold, cough, allergy, bronchodilator and antiasthmatic ingredients pursuant to § 330.10(a)(1):

Francis C. Lowell, M.D., Chairman
Hylan A. Bickerman, M.D.
Halla Brown, M.D.
Robert K. Chalmers, Ph.D.
Mary Jo Reilly, M.S.
James R. Tureman, M.D.
Colin R. Woolf, M.D.

The Panel was first convened on November 6, 1972, in an organizational meeting. Working meetings were held on December 11 and 12, 1972; January 23 and 24, February 28 and March 1, April 5 and 6, May 10 and 11, June 19 and 20, September 25 and 26, October 31 and November 1, December 6 and 7, 1973; January 8 and 9, March 19 and 20, June 12 and 13, September 11 and 12, October 31, November 1, December 3 and 4, 1974; January 30 and 31, April 3, 4 and 5, May 15 and 16, July 17 and 18, September 24 and 25, November 19, 20 and 21, and December 17, 18 and 19, 1975; February 2, and March 2 and 3, 1976.

Two nonvoting liaison representatives served on the Panel. Mrs. Anita Ohlhausen, nominated by an ad hoc group of consumer organizations, served as the consumer liaison and Joseph L. Kanig, Ph. D., nominated by the Proprietary Association, served as the industry liaison. The following employees of the Food and Drug Administration served: Anna L. Standard, M.D., Executive Secretary until March 26, 1974 followed by Joel Aronson, R. Ph.; Thomas D. DeCillis, R. Ph., Panel Administrator; Recie Bomar, R. Ph., Drug Information Analyst until February, 1973 followed by Lloyd G. Scott, R. Ph. until May, 1974 followed by Gary P. Trosclair, R. Ph.

In addition to the Panel members and liaison representatives, the following individuals were given an opportunity to appear before the Panel to express their views either at their own or at the Panel's request:

Paul Bass, Ph. D.
C. Warren Bearman, M.D.
John Behrman, M.D.
Richard C. Brogle, Ph. D.
C. Edward Buckley III, M.D.
A. Lee Caldwell, Jr., Ph. D.
Robert B. Choate
Sanford Chodosh, M.D.
John T. Connell, M.D.
Joseph Dresner
Constantine Falliers, M.D.
Arthur D. Flanagan, M.D.
Spencer Free, Ph. D.
Arthur Grollman, M.D.
Robert M. Hodges
George F. Hoffnagle, Sc. D.
Clarence Imboden, M.D.
Charles Janeway, M.D.
Anita Johnson, Esq.
Stuart J. Land, Esq.
Ben Marr Lanman, M.D.
Vincent D. Larkin, M.D.
Louie G. Linarelli, M.D.
Jennifer Loggie, M.D.
S. J. London, M.D.
Leslie M. Lueck, M.D.
Guillermo Martinez
John McLean, M.D.
Fletcher B. Owen, M.D.
Elias W. Packman, Sc. D.
Joseph Page, Esq.
Joseph J. Pittelli, M.D.
William R. Pool
Thomas W. Richards, M.D.
Norman Salik, M.D.
Robert T. Scanlon, M.D.
Daniel L. Shaw, Jr., M.D.
Alex Silverglade, M.D.
Joseph Smith, M.D.
Alfred E. Sutherland, Esq.
Garret W. Swenson, Esq.
M. L. Thomson, M.D.
Sumner Yaffee, M.D.

No person who so requested was denied an opportunity to appear before the Panel.

The Panel has thoroughly reviewed the literature, and the various data submissions, has listened to additional testimony from interested parties and has considered all pertinent data and information submitted through March 3, 1976 in arriving at its conclusions and recommendations.

In accordance with the OTC drug review regulations (21 CFR 330.10), the Panel's findings with respect to these classes of drugs are set out in three categories:

Category I. Conditions under which cold, cough, allergy, bronchodilator and antiasthmatic products are generally recognized as safe and effective and are not misbranded.

Category II. Conditions under which cold, cough, allergy, bronchodilator and antiasthmatic products are not generally recognized as safe and effective or are misbranded.

Category III. Conditions for which the available data are insufficient to permit final classification at this time.

The Panel recommends the following for each group of drugs:

1. That the conditions included in the monograph on the basis of the Panel's determination that they are generally recognized as safe and effective and are not misbranded (Category I) be effective 30 days after the date of publication of the final monograph in the FEDERAL REGISTER.

2. That the conditions excluded from the monograph on the basis of the Panel's determination that they would result in the drug not being generally recognized as safe and effective or would result in misbranding (Category II) be eliminated from OTC drug products effective 6 months after the date of publication of the final monograph in the FEDERAL REGISTER, regardless of whether further testing is undertaken to justify their future use.

3. That the conditions excluded from the monograph on the basis of the Panel's determination that the available data are insufficient (Category III) to classify such conditions either as Category I—generally recognized as safe and effective and not misbranded; or as Category II not being generally recognized as safe and effective or would result in misbranding, be permitted to remain in use for a period of time justified in the report of 2, 3, 4 or 5 years for the specific conditions after the date of publication of the final monograph in the FEDERAL REGISTER, if the manufacturer or distributor of any such drug utilizing such conditions in the interim conducts tests and studies adequate and appropriate to satisfy the questions raised with respect to the particular condition by the Panel.

I. Submission of Data and Information

Pursuant to the notice published in the Federal Register of August 9, 1972 (37 FR 16029) requesting the submission of data and information on cold, cough, allergy, bronchodilator and antiasthmatic (CCABA) drugs, the following firms made submissions relating to the indicated products:

A. SUBMISSIONS BY FIRMS

Firm	*Marketed products*
Abbott Laboratories, North Chicago, Ill. 60064.	Calcidrine Syrup, Quelidrine Cough Syrup.
Block Drug Co., Inc., Jersey City, N.J. 07302.	BC All Clear.
Boericke & Tafel, Inc., Philadelphia, Pa. 19107.	B & R Dictan Cough Syrup, B & R Tablets No. 241.
Breon Laboratories, Inc., New York, N.Y. 10016.	Bronkotabs, Bronkotabs-HAFS, Broncholixir.
Calgon Consumer Prod., Co., Inc., Pittsburgh, Pa. 15230.	Sucrets Cold Decongestant Formula, Sucrets Cough Control Formula, Sucrets Sore Throat Lozenges.
Chesebrough-Pond's, Inc., Trumbull, Conn. 06611.	Cold-Team-24 Daytime Tablets, Cold-Team-Nighttime Liquid, Pertussin 8-Hour Cough Formula, Pertussin Medicated Vaporizer, Pertussin Plus Night-Time Cold Medicine, Pertussin Wild Berry Cough Syrup.
Ciba-Geigy Corp., Summit, N.J. 07901	Otrivin Nasal Solution, Otrivin Nasal Spray, Otrivin Pediatric Nasal Solution, Otrivin Pediatric Nasal Spray, Privine Nasal Solution, Privine Nasal Spray.
Colgate-Palmolive Co., Piscataway, N.J. 08854.	Congestaid Aerosol.
Creomulsion Co., Atlanta, Ga. 30301	Cough Chek, Colchek, Creomulsion Cough Medicine, Creomulsion Cough Medicine for Children, Creozets Cough and Throat Lozenges.
Dorsey Laboratories, Lincoln, Nebr. 68501	Chexit Tablets, Dor-C Tablets, Dorcol Pediatric Cough Syrup, Triaminic Expectorant, Triaminic Syrup, Triaminicin Nasal Spray, Triaminicin Tablets, Triaminicol Cough Syrup, Tussagesic Suspension, Tussagesic Tablets, and Ursinus Tablets.
The Dow Chemical Co., Zionsville, Ind. 46077.	Novahistine DH, Novahistine Elixir, Novahistine Expectorant, Novahistine Fortis Capsules, Novahistine Melet Tablets, 2/G, and 2G/DM.
Drew Laboratories, New York, N.Y. 10016	Bronkaid Mist, Bronkaid Tablets.
F & F Laboratories, Inc., Chicago, Ill. 60632.	F. & F. Original Formula Cough Lozenges.
Father John's Medicine Co., Inc., Lowell, Mass. 01853.	Father John's Medicine for Cough and Colds.
G. E. Laboratories, Inc., Shamokin, Pa. 17872.	Troutman's Cough Syrup.
Glenbrook Laboratories, New York, N.Y. 10016.	Breacol Decongestant Cough Medication with Neo-Synephrine.
Hall Brothers, Radcliffe, Manchester England.	Hall's Honey-Lemon Cough Drops.
Hall Brothers, Whitefield, Manchester England.	Hall's Cherry Cough Drops.
Hoffman-LaRoche, Inc., Nutley, N.J. 07110.	Theporin, Phenindamine.
The Holford Co., Minneapolis, Minn. 55403	Holford's Famous Inhaler, Indian Chief Inhaler.
Ives Laboratories, Inc., New York, N.Y. 10017.	Cerose, Cerose Compound Cerose-DM, Cetro-Cerose.
Johnson & Johnson, New Brunswick, N.J. 08903.	Sine-Aid.
Key Pharmaceuticals, Inc., Miami, Fla. 33169.	Key Tusscapine.
Knoll Pharmaceutical Co., Whippany, N.J. 07981.	Verequad Suspension, Verequad Tablets.
LaMay's Asthma Eze, Inc., Kalaska, Mich. 49646.	Asthma Eze.
Luden's, Inc., Reading, Pa. 19601	Luden's Honey Lemon Cough Drops, Luden's Honey Licorice Cough Drops, Luden's Menthol Cough Drops, Luden's Menthol Eucalyptus Cough Drops, Luden's Wild Cherry Cough Drops.
Menley & James Laboratories, Philadelphia, Pa. 19101.	Contac.
The Metholatum Co., Inc., Buffalo, N.Y. 14213.	Mentholatum Ointment.
Merck and Co., Inc., Rahway, N.J. 07065	Nectadon.
Merck Sharp & Dohme, West Point, Pa. 19486.	Propadrine Capsules 25 mg, Propadrine Capsules 50 mg, Propadrine Elixir.
Miles Laboratories, Inc., Elkhart, Ind. 46514.	Alka-Seltzer Plus Cold Tablets.
Monsanto Co., St. Louis, Mo. 63166	Methapyrilene Fumarate, Methapyrilene Hydrochloride.
McNeil Laboratories, Inc., Fort Washington, Pa. 19034.	Co-Tylenol Cold Formula.

Mitchum-Thayer, Inc., New York, N.Y. 10020	Arrestin Extra Strength Cough Medicine with D-Methorphan, Asthma-Nefrin Solution "A" Inhalant, AsthmaNefrin Automatic Aerosol Mist, AsthmaNefrin Capsules, Liquiprin Nighttime Cold Medicine for Children.
Norwich Products, Norwich, N.Y. 13815	Norwich Baby Cough Syrup, Norwich Terpin Hydrate and Dextromethorphan Hydrobromide Elixir N.F., Quadrin Decongestive Tablets.
Parke-Davis & Co., Detroit, Mich. 48232	Benylin Cough Syrup, Benadryl.
S. B. Penick & Co., New York, N.Y. 10007	Glyceryl Guaiacolate.
Pfipharmecs Pfizer Pharmaceuticals, New York, N.Y. 10017.	Toclase Cough Syrup, Toclase Cough Tablets.
Pharmacraft, Rochester, N.Y. 14603	Allerest Allergy Tablets, Allerest Nasal Spray, Allerest Time Capsules, Children's Allerest Allergy Tablets, Sinarest.
Plough, Inc., Memphis, Tenn. 38101	St. Joseph Cough Syrup for Children.
Reid-Provident Laboratories, Inc., Atlanta, Ga. 30308.	Coton Syrup, Histalet-DM, Reidacol, Tusstrol, Tusstrol-DM.
A. H. Robins Co., Richmond, Va. 23220	Dimetane Elixir, Dimetane Tablets, Robitussets Troches, Robitussin, Robitussin-DM Cough Calmers, Robitussin-DM, Robitussin-PE Decongestant Expectorant.
Roerig, New York, N.Y. 10017	Coryban-D Cold Capsules, Coryban-D Cough Syrup, Coryban-D Nasal Spray.
Sandoz Pharmaceuticals, E. Hanover, N.J. 07936.	Flogesic.
Sauter Labs., Inc., Nutley, N.J. 07110	Children's Romilar Cough Syrup, Romilar CF Capsules, Romilar CF Syrup, Romilar CF 8-Hour Cough Formula, Romilar Chewable Cough Tablets for Children, Romilar Cough and Cold Capsules, Romilar Cough Discs, Romilar Expectorant, Romilar Hydrobromide Tablets, Romilar Syrup, Romilar III Cough Syrup with Expellin.
G. D. Searle & Co., Chicago, Ill. 60680	Amodrine.
Schering Corp., Bloomfield, N.J. 07003	Afrin Decongestant Nasal Spray, Afrin Decongestant Nose Drops, Chlor-Trimeton Antihistamine Syrup, Chlor-Trimeton Antihistamine Tablets, Coricidin "D" Tablets, Children's Coricidin Demilets Tablets, Children's Coricidin Medilets, Coricidin.
R. Schiffmann Co., Los Angeles, Calif. 90031	Asthmador.
Smith, Kline, & French Laboratories, Philadelphia, Pa. 19101.	Benzedrex Inhaler, Ornacol Cough and Cold Capsules, Ornacol Cough and Cold Liquid, Ornex, Toryn Syrup, Toryn Tablets.
E. R. Squibb & Sons, Inc., New Brunswick, N.J. 08903.	Spec-T Anesthetic Lozenges, Spec-T Sore Throat Decongestant Lozenges, Spec-T Sore Throat Spray, Spec-T Sore Throat Cough Suppressant Lozenges.
Sterling Products International, New York, N.Y. 10016.	Breacol with Prylon.
Templetons, Inc., Buffalo, N.Y. 14223	Raz-Mah Greys Capsules.
Henry Thayer Co., Cambridge, Mass. 02138	Thayers Slippery Elm Throat Lozenges, Thayers Slippery Elm Throat Lozenges (Wild Cherry).
Thayer Labs, Inc., Cambridge, Mass. 02138	AsthmaNefrin Syrup.
The Upjohn Co., Kalamazoo, Mich. 49001	Cheracol Cough Syrup, Cheracol D Cough Syrup, Cidicol Syrup, Elixir Terpin Hydrate and Codeine N.F., Elixir Terpin Hydrate and Codeine Sulfate, Emeracol Cough Syrup, Hydriodic Acid Cough Syrup, Aromatic Iodized Lime Expectorant Tablets, Orthoxicol Cough Syrup, Pyrroxate Capsules, Pyrroxate Tablets, Special Formula No. 2 Analgesic Antipyretic Tablets.
Vick Chemical Co., New York, N.Y. 10017	Vicks NyQuil Nighttime Colds Medicine, Vicks Cough Silencers, Vicks Cough Syrup, Vicks Formula 44 Cough Discs, Vicks Formula 44 Cough Mixture, Vicks Formula 44-D Cough Mixture, Vicks Inhaler, Vicks Medicated Cough Drops (Blue Mint), Vicks Medicated Cough Drops (Menthol-Eucalyptus), Vicks Medicated Cough Drops (Regular), Vicks Medicated Cough Drops (True Lemon), Vicks Medicated Cough Drops (Wild Cherry), Vicks Sinex Decongestant Nasal Spray, Vicks Vaporub, Victors Menthol-Eucalyptus Dual Action Cough Drops and Victors Menthol-Eucalyptus Dual Action Cough Drops (Cherry), Vicks Vaporub, Vicks Vaposteam, Oil of Turpentine, Doxylamine Succinate.

Warner-Chilcott Laboratories, Morris Plains, N.J. 07950.	Tedral Tablets, Tedral Anti-H Tablets, Tedral Pediatric Suspension.
Warner-Lambert Co., Morris Plains, N.J. 07950.	Listerine Big 4 Cough Formula, Hall's Mentho-Lyptus Cough Tablets, Listerine Antiseptic, Listerine Antiseptic Throat Lozenges (lemon-mint), Listerine Antiseptic Throat Lozenges (orange), Listerine Antiseptic Throat Lozenges (regular), Listerine Cold Tablet, Listerine Cough Control Lozenges, Smith Brothers Medicated Cough Drops (black licorice), Smith Brothers Medicated Cough Drops with Benzocaine (minted menthol), Smith Brothers Medicated Cough Drops (Wild Cherry), Super Anahist Decongestant Tablets, Super Anahist Decongestant Nasal Spray.
Whitehall Laboratories, Inc., New York, N.Y. 10017.	Bronitin Tablets, Bronitin Mist, Clear & Dry Sinus Clearant Tablets, Dondril Anticough Tablets, Dristan Decongestant Tablets, Dristan Capsules, Dristan Nasal Mist, Dristan Decongestant Vapor Nasal Spray, Primatene M Formula Tablets, Primatene Mist, Primatene P Formula Tablets, Dristan Decongestant Cough Formula.
Winthrop Laboratories, New York, N.Y. 10016.	Neo-Synephrine Compound Decongestant Cold Tablets, Neo-Synephrine HCl Decongestant Elixir, Neo-Synephrine HCl Jelly, Neo-Synephrine Nasal Spray ¼ percent, Neo-Synephrine Nasal Spray ½ percent, Neo-Synephrine Decongestant Nose Drops ⅛ percent, Neo-Synephrine Decongestant Nose Drops ¼ percent, Neo-Synephrine Decongestant Nose Drops ½ percent, Neo-Synephrine Decongestant Nose Drops 1 percent, NTZ Nasal Spray, NTZ Decongestant Nose Drops, Synephricol Antihistaminic Cough Syrup.
Winthrop Products, Inc., New York, N.Y. 10016.	NRT Antihistaminic Decongestant, NRT Nasal Spray, Asafen Tablets, Deka Expectorant Cough Syrup, NTR Decongestant Antihistaminic, NTR Nasal Spray, Recindal, Synephricol Cold Tablets, Neosynephrine Intranasal Drops ¼ percent, Neosynephrine Intranasal Drops 1 percent.
Wyeth Laboratories, Philadelphia, Pa. 19101.	Phenergan.

In addition, the following firms or groups made related submissions:

Firm	*Submissions*
Bristol-Myers Products, New York, N.Y. 10022.	Phenylephrine hydrochloride, Phenylpropanolamine.
Chattem Drug & Chemical Co., Chattanooga, Tenn. 37409.	Theophylline sodium glycinate.
Lilly Research Laboratories, Indianapolis, Ind. 46206.	Methapyrilene hydrochloride.
Miles Laboratories, Inc., Elkhart, Ind. 46514.	Phenylpropanolamine salts.
Parke Davis & Co., Detroit, Mich. 48232.	Diphenhydramine and pseudoephedrine.
A. H. Robins, Richmond, Va. 23220.	Glyceryl guaiacolate.
Smith, Kline & French Laboratories, Philadelphia, Pa. 19101.	Chlorpheniramine, Brompheniramine maleate, Phenylpropanolamine, propylhexedrine, caramiphen edisylate.
Linda Taliaferro, Austin, Tex. 78712.	Stramonium-belladonna.
Vick Chemical Co., New York, N.Y. 10017.	Topical ephedrine, doxylamine succinate, xylometazoline hydrochloride.
Vick Division Research, Mount Vernon, N.Y. 10553.	Alcohol.
Whitehall Laboratories, Inc., New York, N.Y. 10017.	Oral phenylephrine, and oral phenindamine.
Wyeth Laboratories, Inc., Philadelphia, Pa. 19101.	Promethazine hydrochloride.

D. LABELED INGREDIENTS CONTAINED IN MARKETED PRODUCTS SUBMITTED TO THE PANEL

Acetaminophen (*N*-acetyl-*p*-aminophenol)
Acetic acid
N-acetyl-*p*-aminophenol (acetaminophen)
Alcohol
Alkyl dimethyl benzylammonium chloride (benzalkonium chloride)
Aloin
Aluminum hydroxide-magnesium carbonate co-dried gel
Aminophylline
Ammonium chloride
Anethole
Anise
Antimony potassium tartrate
Ascorbic acid (vitamin C)
Aspirin
Atropine sulfate
Banana arome
Beechwood creosote
Belladonna
Belladonna alkaloids
Benzalkonium chloride (alkyl dimethyl benzylammonium chloride)
Benzocaine
Benzyl alcohol
Benzaldehyde
Blood root
Boric acid
Bornyl acetate
Brompheniramine maleate
Bryonia tincture
Caffeine
Calcium carbaspirin
Calcium iodide anhydrous (iodides)
Camphor
Capsicum
Caramel
Caramiphen edisylate (caramiphen ethanedisulfonate)
Caramiphen ethanedisulfonate (caramiphen edisylate)
Carbetapentane citrate
Cascara
Cedar leaf oil
Cedar, natural
Cetalkonium chloride
Cetylpyridinium chloride
Cherry flavoring
Cherry nut flavoring
Chlorobutanol
Chloroform
Chlorpheniramine maleate
Citric acid
Citric acid (hydrate)
Cocillana
Cod liver oil
Codeine
Codeine alkaloid
Codeine phosphate
Codeine sulfate
Compound white pine syrup
1-Desoxyephedrine
Dextromethorphan
Dextromethorphan hydrobromide
Dextrose
Dioctyl sodium sulfosuccinate
Diphenhydramine hydrochloride
Dipropylene glycol
Disodium edetate
Doxylamine succinate
Drosera tincture
Elm bark
Ephedrine
Ephedrine hydrochloride
Ephedrine sulfate
Epinephrine
Epinephrine bitartrate
Epinephrine hydrochloride (racemic)
Eriodictyon fluid extract (yerba santa)
Ethylmorphine hydrochloride
Eucalyptol
Eucalyptus oil
Euphorbia pilulifera
Exract white pine compound
F. E. Horehound
Fluidextract ipecac (ipecac fluidextract)
Glycerin
Glyceryl guaiacolate
Glycyrrhiza (licorice)
Grape flavoring
Grindelia
Gum arabic
Hexylresorcinol
Honey
Hydriodic acid (iodides)
Hydrocodone bitartrate
Hyoscyamine sulfate
Iodides (calcium iodide anhydrous, hydriodic acid syrup, iodized lime, potassium iodide)
Iodized lime (iodides)
Ipecac
Ipecac fluidextract (fluidextract ipecac)
Lemon oil
Licorice (glycyrrhiza)
Lobelia
Lobelium
Menthol/peppermint oil
Methapyrilene fumarate
Methapyrilene hydrochloride
Methoxyphenamine hydrochloride
Methylcellulose
Methylparaben

Methyl salicylate
Monocalcium phosphate
Mustard oil
Myristica oil
Naphazoline hydrochloride
Noscapine
Noscapine hydrochloride
Oil of pine
Oleyl alcohol
Oxymetazoline hydrochloride
Peppermint oil/menthol
Petrolatum base
Phenacetin
Phenindamine tartrate
Pheniramine maleate
Phenobarbital
Phenylephrine bitartrate
Phenylephrine hydrochloride
Phenylmercuric acetate
Phenylpropanolamine hydrochloride
Phenylpropanolamine bitartrate
Phenylpropanolamine maleate
Phenyltoloxamine citrate
Pineapple flavoring
Pine tar
Podophyllum resin
Potassium guaiacolsulfonate
Potassium nitrate
Promethazine hydrochloride
Propylhexedrine
Propylparaben
Pseudoephedrine sulfate
Pyrilamine maleate
Quinine sulfate
Racemic epinephrine hydrochloride
Racephedrine hydrochloride
Rumex
Salicylamide
Saline phosphate buffer solution
Scopolamine hydrobromide
Sodium bicarbonate
Sodium bisulfite
Sodium citrate
Spirits of turpentine (turpentine oil)
Squill extract
Sticta pulmonaria
Stramonium
Sucrose
Sugar
Sugar base
Syrup base
Terpin hydrate
Thenyldiamine hydrochloride
Theophylline
Theophylline anhydrous
Theophylline calcium salicylate
Thimerosal
Thonzonium bromide
Thonzylamine hydrochloride
Thymol
Tincture of benzoin
Tolu
Tolu balsam
Tolu balsam tincture
Triethylene glycol
Vegetable stearate
Vitamin C (ascorbic acid)
White pine
Wild cherry
Wild cherry fluid extract
Yerba santa (eriodictyon fluid extract)
Xylometazoline hydrochloride

Ingredients reviewed by the Panel in addition to the submitted data:

Ipecac syrup
Potassium iodide (iodides)
Theophylline sodium glycinate

C. CLASSIFICATION OF INGREDIENTS

1. Active ingredients. The Panel has classified the following ingredients submitted to the Panel into groups identified below:

ANTITUSSIVES

Beechwood creosote
Camphor
Caramiphen edisylate (caramiphen ethanedisulfonate)
Caramiphen ethanedisulfonate (caramiphen edisylate)
Carbetapentane citrate
Cod liver oil
Codeine
Codeine alkaloid
Codeine phosphate
Codeine sulfate
Dextromethorphan
Dextromethorphan hydrobromide
Diphenhydramine hydrochloride
Elm bark
Ethylmorphine hydrochloride
Eucalyptol/eucalyptus oil
Horehound
Horehound (horehound fluid extract)
Hydrocodone bitartrate (dihydrocodeinone)
Menthol/peppermint oil
Noscapine
Noscapine hydrochloride
Thymol
Turpentine oil (spirits of turpentine)

EXPECTORANTS

Ammonium chloride
Antimony potassium tartrate
Beechwood creosote
Camphor
Chloroform
Compound benzoin tincture
Compound white pine syrup
Eucalyptol/eucalyptus oil
Extract white pine compound
Glyceryl guaiacolate
Iodides (calcium iodide anhydrous, hydriodic acid syrup, iodized lime, potassium iodide)
Ipecac fluidextract
Ipecac syrup
Menthol/peppermint oil
Pine tar
Potassium guaiacolsulfonate
Sodium citrate
Squill
Squill extract
Syrup of pine tar
Terpin hydrate
Terpin hydrate elixir
Tincture of benzoin
Tolu
Tolu balsam
Tolu balsam tincture
Turpentine oil (spirits of turpentine)
White pine

BRONCHODILATORS

SYMPATHOMIMETIC AMINES

Belladonna alkaloids
Ephedrine
Ephedrine hydrochloride
Ephedrine sulfate
Epinephrine
Epinephrine bitartrate
Epinephrine hydrochloride (racemic)
Methoxyphenamine hydrochloride
Pseudoephedrine hydrochloride
Pseudoephedrine sulfate
Racephedrine hydrochloride

THEOPHYLLINES

Aminophylline
Theophylline anhydrous
Theophylline calcium salicylate
Theophylline sodium glycinate

MISCELLANEOUS

Euphorbia pilulifera

ANTICHOLINERGICS

Atropine sulfate
Belladonna
Belladonna alkaloids
Hyoscyamine sulfate
Scopolamine hydrobromide
Stramonium

ANTIHISTAMINES

Brompheniramine maleate
Chlorpheniramine maleate
Diphenhydramine hydrochloride
Doxylamine succinate
Methapyrilene fumarate
Methapyrilene hydrochloride
Phenindamine tartrate
Pheniramine maleate
Phenyltoloxamine citrate
Promethazine hydrochloride
Pyrilamine maleate
Thenyldiamine hydrochloride
Thonzylamine hydrochloride

NASAL DECONGESTANTS

Beechwood creosote
Bornyl acetate
Camphor
Cedar leaf oil
1-Desoxyephedrine
Ephedrine
Ephedrine hydrochloride
Ephedrine sulfate
Eucalyptol/eucalyptus oil
Menthol/peppermint oil
Mustard oil (allylisothiocyanate)
Naphazoline hydrochloride
Oxymetazoline hydrochloride
Phenylephrine hydrochloride
Phenylpropanolamine hydrochloride
Phenylpropanolamine bitartrate
Phenylpropanolamine maleate
Propylhexedrine
Pseudoephedrine hydrochloride
Pseudoephedrine sulfate
Racephedrine hydrochloride
Thenyldiamine hydrochloride
Thymol
Turpentine oil (spirits of turpentine)
Xylometazoline hydrochloride

2. Miscellaneous labeled ingredients:

Antihistamines with sleep-aid claims
Ascorbic acid (vitamin C)
Caffeine
Phenobarbital
Vitamins

3. Ingredients submitted to the Panel and classified as inactive and/or pharmaceutical necessary ingredients:

Acetic acid
Alcohol
Alkyl dimethyl benzylammonium chloride (benzalkonium chloride)
Aluminum hydroxide—magnesium carbonate (co-dried gel)
Anethole
Anise
Banana arome
Benzaldehyde
Benzalkonium chloride (alkyl dimethyl benzylammonium chloride)
Blood root
Bryonia tincture
Caramel
Cedar, natural
Cetalkonium chloride
Cetylpyridinium chloride
Cherry flavoring
Cherry nut flavoring
Chlorobutanol
Chloroform (0.4% maximum)
Citric acid
Citric acid (hydrate)
Cocillana
Dextrose
Dipropylene glycol
Disodium edetate
Drosera tincture
Eriodictyon fluidextract (yerba santa)
Glycerin
Glycyrrhiza (licorice)
Grape flavoring
Grindelia
Gum arabic

Honey
Lemon oil
Licorice (glycyrrhiza)
Lobelia
Lobelium
Methyl cellulose
Methylparaben
Monocalcium phosphate
Myristica oil
Oleyl alcohol
Petrolatum base
Phenylmercuric acetate
Pineapple flavoring
Potassium nitrate
Propylparaben
Rumex
Saline phosphate buffer solution
Sodium bisulfite
Sticta pulmonaria
Sucrose
Sugar
Sugar base
Syrup base
Thimerosol
Thonzonium bromide
Triethylene glycol
Vegetable stearate
Wild cherry
Wild cherry fluidextract
Yerba santa (eriodictyon fluidextract)

4. Ingredients submitted to the Panel and deferred to other OTC advisory review panels.

a. Ingredients deferred to the Advisory Review Panel on OTC internal analgesic including antirheumatic drug products:

(1) Acetaminophen (*N*-acetyl-*p*-aminophenol)
(2) *N*-acetyl-*p*-aminophenol (acetaminophen)
(3) Aspirin
(4) Calcium carbaspirin
(5) Phenacetin
(6) Quinine sulfate
(7) Salicylamide

b. Ingredients deferred to the Advisory Review Panel on OTC laxative, antidiarrheal, emetic and antiemetic drug products:

(1) Aloin
(2) Cascara
(3) Dioctyl sodium sulfosuccinate
(4) Podophyllum resin

c. Ingredients deferred to the Advisory Review Panel on OTC topical analgesic, antirheumatic, otic, burn, and sunburn treatment and prevention drug products:

(1) Benzocaine
(2) Benzyl alcohol
(3) Boric acid
(4) Capsicum
(5) Methyl salicylate

d. Ingredients deferred to the Advisory Review Panel on OTC oral cavity drug products:

(1) Hexylresorcinol
(2) Methyl salicylate

e. Ingredient deferred to the Advisory Review Panel on antacid drug products:

(1) Sodium bicarbonate

II. General Statements and Recommendations

A. General Comment

The OTC cold, cough, allergy, bronchodilator and antiasthematic Panel was charged with the review and the evaluation of safety and effectiveness data on cold, cough, allergy, bronchodilator, and antiasthmatic ingredients and combinations thereof, the adequacy of their labeling, and to advise the Commissioner of Food and Drugs on the promulgation of monographs establishing conditions under which these over-the-counter (OTC) drug products are generally recognized as safe and effective and not misbranded. The Panel also served as a forum for the exchange of views regarding the prescription or nonprescription status of these various active ingredients and combinations thereof. Panel members were expected to call upon their own expert knowledge and experience in carrying out each element of this charge. Specifically the Panel was charged with the following:

1. Review and evaluation of all data made available to the panel members concerning the safety and effectiveness of cold, cough, allergy, bronchodilator and antiasthmatic treatment and prevention agents, and combinations thereof, utilized in these OTC drug products.

2. Advising the Food and Drug Administration as to the adequacy of the labeling of such cold, cough, allergy, bronchodilator and antiasthmatic treatment and prevention drug products and to make recommendations as to the contents of future labeling of such products.

3. Making recommendations to the Food and Drug Administration regarding those ingredients, their amounts, and combinations thereof, which, based upon the available data, could be considered safe and effective for the above stated uses. These recommendations must be in keeping with agency stated definitions of the terms "safe" and "effective" and in keeping with the agency OTC drug combination policy (21 CFR 330.10(a)(4)(iv)).

4. Making recommendations to the Food and Drug Administration regarding those ingredients, their amounts, and combinations thereof, which based upon the available data, are not considered as safe and effective for the above stated uses. The same criteria must apply as in the determinations of those ingredients which are found to be safe and effective.

5. Advising the Food and Drug Administration regarding those ingredients which in their judgment are likely to be safe and effective, but for which more data are needed. In such cases the Panel was requested to give some guidance as to what type of studies and the maximum time period they feel would be adequate to produce such information for future consideration by the Food and Drug Administration.

6. Advising the Food and Drug Administration on the promulgation of a monograph or monographs establishing conditions under which these OTC drug products are generally recognized as safe and effective and not misbranded. This information is submitted in the form of a written report by the Panel containing the following basic recommendations:

a. Listing of the acceptable active ingredients, singly or combinations thereof.

b. Acceptable dosage ranges of these active ingredients and their combinations.

c. A statement of the acceptable indications for use.

d. Recommended labeling guidelines—warnings, precautions, contraindications, directions for use.

B. Diseases and Related Symptoms Relieved by OTC Cold, Cough, Bronchodilator and Antiasthmatic Products

The Panel makes the following statements and recommendations concerning the symptoms related to the use of antitussives, expectorants, bronchodilators, anticholinergics, antihistamines and nasal decongestants. The symptoms which these drugs may be expected to relieve are those occurring in certain allergic states such as hay fever, asthma, and symptoms in the nose, eyes, sinuses and throat caused by the common cold and other mild respiratory infections. It must be kept in mind that the ingredients and combinations reviewed are not intended to cure but are OTC drugs to provide symptomatic relief.

The Panel has prepared the following table which lists symptoms and the acceptable corresponding pharmacologic groups of drugs for the treatment of these symptoms:

Symptom	*Pharmacologic group*
1. Bronchospasm or asthma	Bronchodilators (sympathomimetic amines, theophyllines)—with the Category I labeling indications recommended by the Panel. (See pt. V. par. B.1. below—Labeling.)
2. Cough	Antitussives—with the Category I labeling indications recommended by the Panel. (See pt. III. par. B.1. below—Labeling.) Expectorants—with the Category I labeling indications recommended by the Panel. (See pt. IV. par. B.1. below—Labeling.).
3. Runny nose	Anticholinergics—with the Category I labeling indications recommended by the Panel. (See pt. VI. par. B.1. below—Labeling.)
4. Nasal congestion	Nasal decongestants—with the Category I labeling indications recommended by the Panel. (See pt. VIII. par. B.1. below—Labeling.)
5. Sinus congestion	Do. Analgesics—with the Category I labeling indications recommended by the OTC Internal Analgesic Panel.
6. Sneezing, watery eyes, and itchy eyes	Antihistamines—with the Category I labeling indications recommended by the Panel. (See pt. VII. par. B.1. below—Labeling.)
7. Sore throat	Analgesics—with the Category I labeling indications recommended by the OTC Internal Analgesic Panel. Local anesthetics—with the Category I labeling indications recommended by the OTC Oral Cavity Panel.
8. Generalized aching	Analgesics—with the Category I labeling indications recommended by the OTC Internal Analgesic Panel.
9. Fever	Antipyretics—with the Category I labeling indications recommended by the OTC Internal Analgesic Panel.

1. *Allergy.* Allergy is a complex of symptoms which arises under circumstances when a person who has acquired a hypersensitivity to a substance encounters that substance. Although one may be born with a tendency to become allergic, one must be exposed to a substance for weeks, months or years before one actually becomes allergic to it. Probably about 15 percent or more of the population becomes significantly allergic. Substances to which people ordinarily become allergic are pollens, mold spores, animal dander and certain dusts and sprays in the home and in industry. These are airborne and are inhaled. One may also become allergic to certain foods and drugs and to substances coming in contact with the skin such as drugs and poison ivy (poison oak). Substances to which people become allergic are called allergens. In our highly industrial and technological society we are increasingly exposed to allergens never encountered by our forebears; for this reason, the number of persons with allergies is rising and may continue to rise.

The allergic symptoms with which the Panel is concerned are nasal (sneezing, watery or mucous discharge, itching and obstruction), and bronchial (cough, bronchospasm and expectoration). Another manifestation of allergy is itchy and watery eyes. Allergy of this type belongs to a subgroup of the so-called "immune" class of disease termed "atopy." In this class of disease an antibody mediates the reaction. The antibody belongs to the IgE class of immunoglobulins which has the peculiarity of attaching itself to a certain type of cell (mast cells in the tissues and basophils in the blood). With the arrival of the allergen, union between the allergen and the antibody attached to these cells occurs and leads to the release of substances which in turn cause the symptoms we call "allergic." One of the substances released, and perhaps the principal one, is histamine. The antihistaminic drugs block the action of histamine.

Identification and elimination of the offending substance (allergen) are the measures of choice. However, these are often impossible to achieve. The proper use of OTC products containing antihistamines, sympathomimetics, or theophyllines may provide relief of allergy symptoms. Although OTC drugs are often adequate for relief, the allergic reaction may be so intense that OTC drugs are not adequate and other measures, such as epinephrine by injection, and corticosteroids, requiring the supervision of a physician are needed. In the case of allergy to pollens and some other inhaled allergens, symptoms can be lessened or eliminated under medical supervision by a course of injections of suitably prepared allergenic extract.

REFERENCES

(1) Sheldon, J. M., R. G. Lovell and K. P. Mathews, "A Manual of Clinical Allergy," 2d Ed., W. B. Saunders Co., Philadelphia, 1967.

(2) Patterson, R., "Allergic Diseases: Diagnosis and Management," The J. B. Lippincott Co., Philadelphia, 1972.

2. *Asthma and other respiratory diseases and the use of bronchodilators.* Asthma is a disease in which there is widespread narrowing of the airways due to airway wall muscle spasm which occurs in response to various stimuli. Among the stimuli which may lead to asthma is the inhalation of substances such as pollens and animal danders in people who are allergic to these substances. This reaction causes partial obstruction to air flow and shortness of breath. The spasm causing narrowing of the air tubes may subside either spontaneously or as a result of therapy. Airway narrowing occurs also where there is widespread bronchial infection such as in acute or chronic bronchitis, in pulmonary emphysema where there is destruction of the lung tissue, and in pulmonary congestion from failure of the left side of the heart. Asthma is a difficult disease condition for the layman to diagnose and even physicians have difficulty in distinguishing asthma from the above other conditions which cause airway narrowing. Therefore, it is very important that the diagnosis of asthma first be established by a physician before the use of OTC bronchodilator preparations.

Medications which relax the airway muscle spasm and relieve the shortness of breath of asthma are called bronchodilators. Usually these drugs are given by mouth as a tablet or liquid, or they may be inhaled as a spray from a suitable dispenser. The response of mild or even moderate asthma to these drugs is often quick and there is effective relief from shortness of breath. The Panel believes that, when taken as directed, the drugs are safe for OTC use, but undesirable effects can occur. These adverse effects are mainly exhibited as increased rate and force of the heart beat, rise in blood pressure, nervousness and sleeplessness, and nausea or vomiting.

Asthma is a very common disease and it is reasonable to have bronchodilators available on a nonprescription basis so that in mild cases relief may be obtained quickly without the possible delays of obtaining a physician's prescription. However, it is very important that the diagnosis of asthma first be established by a physician as some of the other conditions which resemble asthma, such as pulmonary congestion from failure of the left side of the heart, should not be treated by certain types of bronchodilators. Even the patient with true asthma should be warned that if a bronchodilator does not cause excellent and rapid relief, he should call his physician. The reason he should call his physician is that in a severe and worsening attack of asthma, slight relief may be given by these bronchodilators and this may give a false sense of security. The patient may then postpone seeking medical help or going to a hospital until his disease has reached life-threatening severity. Therefore, labeling of these preparations should be very precise in that the patient should be instructed to seek medical assistance immediately if relief of his symptoms does not occur within a short time of us-

ing the bronchodilator preparation. In the use of epinephrine aerosol, relief should occur within 20 minutes; in the use of ephedrine, methoxyphenamine tablets and tablets of theophylline and its salts, relief should occur within 1 hour.

REFERENCES

(1) Harris, H. W. et al., "Chronic Bronchitis, Asthma and Pulmonary Emphysema. A statement by the Committee on Diagnostic Standards for Nontuberculous Respiratory Disease, American Thoracic Society," *American Review of Respiratory Diseases*, 85:762–768, 1962.

3. *The "common cold" (cold).* The "common cold" (cold) is a self-limited respiratory infection caused by one or more viruses. A cold is rarely serious and is readily transmitted. Throughout this document, the Panel has used the term "common cold" which the Panel considers synonymous with the term "cold."

A "common cold" often begins quite abruptly with soreness or discomfort in the pharynx, sneezing, watery nasal discharge, followed by nasal congestion. The discharge may subsequently become mucoid or purulent. After the first day or two the eyes may become suffused and the voice husky. The nasal congestion intensifies and the sense of smell and taste is often suppressed or absent. Extension into the sinuses may occur as described in the rhinitis statement. Lethargy, some aches and pains and slight fever may be present. The course is variable and may extend for 7 to 14 days. Cough may occur, especially in the later stages.

Early in its course, the cold is indistinguishable from the early stages of measles, rubella, chickenpox, pertussis, cerebrospinal fever, influenza and atypical pneumonia. The cold also closely simulates allergic rhinitis. The physician's main role in the cold is to exclude more serious illness.

There is no generally accepted treatment that can prevent, cure or shorten the course of the "common cold." Treatments which are available only relieve symptoms. Immunity is apparently of short duration since many individuals have one to three colds each year.

4. *Cough.* A cough is the rapid expulsion of air at high velocity from the respiratory airway producing a noise of varying pitch and intensity. Impulses that initiate the cough reflex may arise from many areas within and outside the respiratory tract.

Normally, coughing is produced by stimulation of the sensory endings of the glossopharyngeal and vagus nerves within the mucous membranes of the respiratory tract. This stimulation can be initiated by infection, chemical irritation, the presence of retained secretions, or foreign material blocking the breathing passages. Localized narrowing of the air tubes may play an important role in stimulation of the cough reflex. Cough can also occur from stimulation outside the respiratory tract. For example, if the external ear is tickled, a cough is produced. Cough can be under considerable voluntary control and therefore can be self-suppressed to a degree. Likewise, an individual can initiate a cough at will. Cough occurs in healthy individuals as a mechanism for clearing the airway of any obstructing mucus or inhaled foreign material.

Medications which suppress the act of coughing by reducing the number of coughs and/or the intensity of coughing are known as antitussive drugs. These preparations are administered by mouth in the form of tablets, syrups, elixirs and lozenges, and by inhalation in the form of rubs and vaporizer additives, and when used as directed provide relief from annoying cough. These drugs are generally safe at the dosages recommended for OTC use. However, antitussives derived from narcotics, such as codeine and hydrocodone, commonly cause constipation as a side effect.

The cough is a protective, physiologic reflex occurring in healthy as well as diseased individuals. It is frequently the presenting symptom in a wide variety of pathologic states, ranging from a mild, self-limiting illness to a serious and even fatal disease. In certain disease states such as asthma, chronic bronchitis and cystic fibrosis, the cough reflex is essential in maintaining an open airway by clearing the respiratory passages of excessive secretions. Because of its importance in preserving the function of the lung, by maintaining an open airway, the cough reflex should not be suppressed indiscriminately.

The irritative cough associated with a self-limiting respiratory tract infection is usually viral in nature or follows the inhalation of irritant gases or dusts, and can readily be recognized and serves no useful function. These conditions are usually associated with a dry, hacking, nonproductive cough in which no sputum is expectorated and lends itself to rational self-medication with OTC preparations. On the other hand, the loose, productive type of cough frequently associated with asthma and bronchitis indicates the presence of retained bronchial secretions which could lead to increasing disability if suppressed; and therefore, should not be treated with an antitussive drug. Any cough which persists for longer than 1 week should be investigated by a physician to exclude the presence of an underlying, potentially serious, respiratory disease.

5. *Symptoms of sinus congestion.* Paranasal sinuses are mucous membrane-lined air cavities in the bony structure of the skull which are continuous with the nasal cavity. Impaired sinus drainage due to nasal congestion, e.g., rhinitis of upper respiratory infection or nasal allergy, may result in sinus inflammation (sinusitis) with associated headache and facial pain or tenderness in the region of the affected sinus(es).

Self-medication with an oral or topical nasal decongestant may aid in resolving the problem by diminishing the nasal obstruction which impairs sinus drainage. An orally administered analgesic, e.g., aspirin, acetaminophen, should provide symptomatic relief from headache and pain associated with the sinus congestion. If symptoms persist, intensify and/or are accompanied by fever, a physician should be consulted.

6. *Rhinitis (allergic rhinitis, vasomotor rhinitis).* a. *Allergic rhinitis.* Allergic rhinitis is caused by allergy to airborne allergens including pollens, animal danders, molds and house dust as described elsewhere in this document. (See part II. paragraph B.1. above—Allergy).

The symptoms of allergic rhinitis are sneezing, watery discharge from the nose, nasal stuffiness and obstruction and nasal itching. The eyes may also be involved in which case there is itching, tearing or redness. There may also be puffiness of the eyelids. Less frequently there is headache, itching of the throat and ears and there may be cough. A few patients feel listless or very tired and some describe themselves as feeling generally ill. Hay fever is the familiar example of allergic rhinitis which occurs in persons allergic to pollens.

In addition to rhinitis the paranasal sinuses are frequently involved. This may cause headache usually frontal in distribution or pain or discomfort in the area of the frontal, ethmoid, maxillary or antral sinuses in the front of the face surrounding the nose.

Sneezing may occur irregularly or in paroxysms, more commonly on awaking in the morning, or may be caused by such nonspecific factors as exposure to abrupt changes in temperature or inhalation of particulate matter.

The nasal discharge may be watery in nature, mucoid or purulent. When purulent, bacterial infection is usually assumed to be present. However, this feature is determined by the number of white cells present and not necessarily by the presence of infectious organisms. The nasal discharge of some patients with rhinitis contains such a large number of eosinophils that the discharge acquires a purulent appearance without evidence of infection.

Rhinitis is classically an allergic response to an inhaled allergen, be it pollen, mold or animal dander. However, rhinitis also occurs as the characteristic feature of infections such as the "common cold."

The diagnosis of allergic rhinitis its based on a history of characteristic symptoms as described above and the demonstration by skin testing that the injection of an aqueous extract prepared from the appropriate pollen or allergen will cause within 10 to 20 minutes local redness, a wheal and itching similar to the reaction to the bite of a mosquito. Examination of the nose characteristically but not invariably shows swelling of the internal membranes which are often pearly gray or reddened instead of pink, their normal color.

b. *Vasomotor rhinitis.* There also occurs a form of rhinitis the symptoms of which are not caused by any recognized allergic exposure. This form of rhinitis tends to occur throughout the year with little or no seasonal variation. The condition is usually called vasomotor rhinitis suggesting an abnormal reactivity of the

blood vessels in the nasal lining but in fact the reason for symptoms is unknown. The symptoms of vasomotor rhinitis are the same as those in allergic rhinitis. Skin tests are not helpful in diagnosis.

c. *Treatment of rhinitis symptoms.* The antihistamines are most effective in the treatment of mild allergic rhinitis (such as hay fever). They are less effective in vasomotor rhinitis. These drugs are discussed more completely later in this document. (See part VII. below—Antihistamines.) Nasal decongestants and anticholinergics have also been used in the management of the symptoms of rhinitis. The use of these drugs will be discussed more completely later in this document. (See part VI. below—Anticholinergics and part VIII. below—Nasal Decongestants.)

C. PRINCIPLES APPLICABLE TO COMBINATION PRODUCTS

1. *General combination policy.* Most cold, cough, allergy, bronchodilator and antiasthmatic (CCABA) products currently in the marketplace containing ingredients which the Panel reviewed are promoted or sold to relieve a number of different symptoms. For example, OTC products commonly used for the treatment of the symptoms of the "common cold" include ingredients intended to provide relief of two or more concomitant symptoms such as nasal congestion, running nose, coughing, watery eyes, headache, fever and muscular aches. These products contain more than one active ingredient in order to cover a spectrum of symptoms. Some of these OTC preparations contain ingredients not reviewed by the Panel, e.g., aspirin, which has been deferred to the Advisory Review Panel on OTC internal analgesic including antirheumatic drug products for evaluation of analgesic and antipyretic claims.

In order to clarify the place of combinations in the marketplace, the Panel applied the OTC Drug Review Regulation (21 CFR 330.10(a)(4)(iv)) which states:

> An OTC drug may combine two or more safe and effective active ingredients and may be generally recognized as safe and effective when each active ingredient makes a contribution to the claimed effect(s); when combining of the active ingredients does not decrease the safety or effectiveness of any of the individual active ingredients and when the combination, when used under adequate direction for use, and warnings against unsafe use, provides rational concurrent therapy for a significant proportion of the target population.

The Panel concurs with the regulation and strongly believes that each active ingredient in a combination product must contribute to the claimed effects and that each active ingredient must be necessary for rational therapy of concurrent symptoms. It is the view of the Panel that it is irrational to use a combination product unless each of the contained active ingredients contributes to the effective treatment of at least one of the labeled symptoms for which the combination product is recommended.

The Panel is familiar with the arguments for combination products and at the same time recognizes the disadvantages of fixed-dosage combination products. One major disadvantage commonly expounded is the inability to permit individualized dosage of each active ingredient. The Panel agrees in principle with this argument. However, if the combination product contains only active ingredients at doses of demonstrated safety and effectiveness and all ingredients are necessary for treatment of symptoms, the Panel concludes that certain combinations may offer a convenient and rational approach for relief of concurrent symptoms.

The Panel refers to a recognized source of drug information which notes that cold remedy mixtures are widely used and enjoy a certain amount of acceptance by the medical profession and the laity (Ref. 1). It is the view of the Panel that certain combinations, as established by the Panel are acceptable and summarized below. (See part II. paragraph C.8.b. below—Criterion.) To support this view, the Panel refers to the conclusion in the above-referenced text (Ref. 1) which states "* * * a physician who chooses to prescribe a cold remedy must be certain that the mixture is composed of drugs with known effectiveness, that the ingredients are present in adequate therapeutic amounts, and that they are therapeutically rational for the type and severity of symptoms being treated."

The Panel has established specific criteria for the treatment of symptoms with combination products. Each Category I combination is currently limited to one active ingredient from any one pharmacologic group. The Panel has placed combinations of two active ingredients from the same pharmacologic group in Category III. Each active ingredient must be generally recognized as safe and effective when used alone for the labeled claim(s) and hence make a contribution to the claimed effect(s) of the combination. The acceptable pharmacologic groups included for treatment of symptoms as determined by the Panel differ sufficiently one from another to reduce the likelihood of a competitive or potentiating effect between agents. Therefore, the Panel has recommended only specific combinations be provided and limited to one active ingredient from any one pharmacologic group. The Panel concludes that products containing the combinations of ingredients provided for below are safe and effective. (See part II. paragraph C.8.b. below—Criterion.)

The Panel further concludes that such combinations of ingredients can provide rational concurrent therapy for a significant and existing target population that can benefit from such use. The Panel emphasizes that these combinations must contain adequate directions for use and include warnings against unsafe use. These combinations of ingredients must clearly indicate in their labeling that they are to be used only when the multiple symptoms are present concurrently. It would not be rational for a consumer having only one symptom to take a combination of ingredients intended for treatment of more than one symptom, or containing active ingredient(s) not required for relief of symptoms present in that individual.

2. *Limitation of ingredients in combination products.* The Panel concludes that, in general, the fewer the ingredients in an OTC product, the safer and more rational the therapy. The Panel has discussed the advantages of single ingredient products elsewhere in this document. (See part II. paragraph J. below—Advantages of Single Ingredient Products.) The Panel believes that the interests of the consumer are best served by exposing the user of OTC drugs to the smallest number of ingredients possible at the lowest possible dosage consistent with a satisfactory level of effectiveness. OTC drugs containing safe and effective single active ingredients are preferred to those having multiple active ingredients because with fewer ingredients there is a reduced risk of undesirable additive or synergistic effects.

Single ingredients are also preferred because the ratio in which components exist in a fixed combination may be unsuitable for some individuals. This is due in part to the great variability of reactions and side effects among these persons to the various drugs in the combination. It is also due in part to the inability of such persons to correlate certain side effects with the use of a particular drug when more than one drug is present in a combination. Both points are discussed more fully elsewhere in this document. (See part II. paragraph J. below—Advantages of Single Ingredient Products.)

The Panel believes that single active ingredient preparations should be available in the OTC market to allow the consumer the opportunity of selecting a single drug for a specific symptom or symptoms. As an example, a single active ingredient preparation containing only an antitussive should be available for treatment of cough. Likewise, a single active ingredient preparation containing only an antihistamine should be available for treatment of running nose, sneezing, and watery eyes. It is the Panel's opinion that presently the public has too little choice in selecting an appropriate drug treatment for such symptoms because of the current OTC market scarcity of single drug ingredient preparations.

In fact, of the 339 volumes received as submissions for review by the Panel, only 44 volumes contained data concerning 24 single active ingredients being marketed in 46 products. This represents 24 single active ingredients, out of a total of 152 active ingredients submitted by firms, as being present in marketed OTC CCABA products. The 46 products containing the single active ingredients represent a wide variety of dosage forms which include aerosols, liquids, tablets, syrups, drops, sprays, jellies and elixirs. The Panel has prepared the following table of the 24 single active ingredients marketed alone in CCABA products and submitted to the Panel for review:

MARKETED DRUG PRODUCTS CONTAINING A SINGLE ACTIVE INGREDIENT

Active ingredient	*Dosage form (number of products)*
Products for the relief of asthma:	
Epinephrine hydrochloride	Aerosols (5) and solutions (1).
Products for the relief of cough:	
Ammonium chloride	Drops (1).
Caramiphen ethanedisulfonate	Do.
Carbetapentane citrate	Syrups (1) and drops (1).
Cocillana	Drops (1).
Dextromethorphan	Syrups (2).
Menthol	Drops (2).
Noscapine	Syrups (2) and bulk chemicals—not a marketed drug product (1).
Products for relief of nasal congestion:	
Naphazoline hydrochloride	Drops (1) and sprays (1).
Oxymetazoline hydrochloride	Do.
Phenylephrine	Drops (1).
Phenylephrine hydrochloride	Sprays (2), jellies (1), and elixirs (1).
Phenylpropanolamine hydrochloride	Tablets (2) and liquids (1).
Xylometazoline hydrochloride	Drops (2) and sprays (2).
Products for use as antihistamines:	
Brompheniramine maleate	Tablets (1) and liquids (1).
Chlorpheniramine maleate	Tablets (1) and syrups (1).
Methapyrilene fumarate	Bulk chemicals—not a marketed drug product (1).
Methapyrilene hydrochloride	Bulk chemicals—not a marketed drug product (1).
Promethazine	Liquids (1).
Products for use as an expectorant:	
Glyceryl guaiacolate	Liquids (2).
Hydriodic acid	Liquids (1).
Iodized lime	Tablets (1).
Products for use in relief of sore throat:	
Benzocaine	Lozenges (1).
Hexylresorcinol	Lozenges (3).

The Panel concludes that in light of the numerous CCABA combination products on the market, there appears to be a shortage of single active ingredient products for the consumer to adequately and individually treat a specific symptom. This may or may not be representative of the marketplace but certainly indicates a paucity of single ingredient products. The Panel recommends that this situation be altered so that the public may make a more discriminating selection in the purchasing of OTC drugs. The Panel recognizes the consumer's prerogative for self-medication and believes that this can only be fully realized when single as well as combination products are more readily available.

The Panel is also aware of the inclusion of inactive, i.e., nontherapeutic, ingredients in CCABA preparations. These inactive ingredients are used for various purposes such as preservatives and flavors for specific product formulations. The Panel recognizes that some ingredients may be necessary for marketing purposes. However, the Panel recommends that the safety of inactive ingredients and the advisability of including them in drug products be reviewed by an appropriate body. The Panel further discusses inactive ingredients elsewhere in this document. (See part II. paragraph I. below—Inactive Ingredients.)

In summary, the Panel recommends that marketed products contain only those active and inactive ingredients that are essential to the product.

3. *Combining of active ingredients reviewed by the Panel from different pharmacologic groups.* The Panel is aware of the concept that it may be more convenient to include more than one active ingredient in the same product. Symptoms of the "common cold" or hay fever may include nasal congestion, running nose and coughing. The Panel has determined that if a combination product contains ingredients which are limited to one active ingredient from each representative pharmacologic group, e.g., nasal decongestant, antihistamine and antitussive, each of which is generally recognized as safe and effective when used alone for the specific symptom, e.g., antitussive for cough, the combination is rational and convenient for treatment of concurrent symptoms. The Panel concludes that the combinations of ingredients from pharmacologic groups identified below are safe and effective for a significant proportion of the target population having concurrent symptoms. (See part II. paragraph C.8.b. below—Criterion.)

The Panel clearly desires to avoid the so-called "shotgun approach" for the treatment of symptoms with a combination of ingredients in a single product. However, due to the unique nature of symptoms to be treated by CCABA preparations under consideration by this Panel, such combinations, with restrictions as established by the Panel, are justifiable.

The Panel is aware of a regulation (21 CFR 331.15(b)) providing for the combining of safe and effective (Category I) antacid and nonantacid active ingredients for the treatment of concurrent symptoms. The Panel emphasizes that the regulation provides for combining ingredients with different pharmacologic activities without additional clinical testing of the combination. This concept has been adopted by this Panel for certain combinations that the Panel has classified as Category I.

The Panel believes that these combinations of pharmacologic groups identified as Category I may offer a convenient and rational approach for relief of concurrent symptoms. The Panel has limited such combinations to three pharmacologic groups because it is unable to determine a significant target population which could benefit from a combination product containing greater than three pharmacologic groups. The Panel can find little scientific justification for including four or more pharmacologic groups in the same product since it is improbable that concurrent symptoms of sufficient duration and severity exist to warrant such combinations. As previously noted in the discussion pertaining to the "common cold," the course and symptoms of the disease are variable and may extend for 7 to 14 days. It would appear highly unlikely that at any one time, simultaneous symptoms would be present and of such severity in the course of the disease as to warrant the need for a product containing more than three pharmacologic groups. Therefore, the Panel has determined that combination products containing four or more different pharmacologic groups be classified as Category III. Before such products may be classified as Category I, a significant target population requiring such a combination for the treatment of concurrent symptoms of sufficient duration and severity must be identified.

4. *Combining of active ingredients reviewed by the Panel from the same pharmacologic group.* The Panel is concerned with the marketing of products containing drugs from the same pharmacologic group. Each Category I combination is currently limited to one active ingredient from any one pharmacologic group. The Panel can find little scientific justification for combining more than one active ingredient from the same pharmacologic group in the same product. The Panel is unaware of adequate supportive data which would establish sufficient argument for combining ingredients from the same pharmacologic group. For most products reviewed by the Panel, these ingredients from the same pharmacologic group are present in subtherapeutic doses. There is a lack of data on the effects of full therapeutic doses of ingredients from the same pharmacologic group in combination and therefore such combinations could not be evaluated by the Panel.

As an example, suppose two ingredients from the same pharmacologic group are combined in equal amounts in terms of pharmacologic activity (i.e., each at one-half the therapeutic dose) in the same product. The Panel doubts the justification in assuming that a dose of the product containing one-half the adult dose of each drug will produce an effect equal to one adult therapeutic dose of

either of the ingredients. The Panel is unable to find data to support the theory of the contribution of subtherapeutic doses of each ingredient in the same pharmacologic group in presently marketed combination products submitted for review to the Panel. The Panel is aware of certain combinations, such as "triple sulfas" to reduce the inherent toxicity of administering a single sulfa drug. However, this concept is difficult to relate to CCABA preparations since little evidence was submitted to the Panel demonstrating sufficient need for such combinations of ingredients from the same pharmacologic group.

It is the opinion of the Panel that to provide for combinations containing ingredients from the same pharmacologic group would contribute to the likelihood of undesirable additive or synergistic effects as noted above. (See part II. paragraph C.2. above—Limitation of ingredients in combination products.) It is accepted medical practice to give only those drugs necessary for the safe and effective treatment of the patient. The Panel believes that this concept should also apply to self-medication where a consumer treats symptoms without the advice of a physician.

In conclusion, to allow for the possibility, however unlikely, that there may be advantages to combining two drugs from the same pharmacologic group, the Panel has determined that such combination(s) be classified as Category III. Additional studies as described below in Principle No. 10 are needed for Category III combinations to determine their safety and effectiveness. (See part II. paragraph 10. below—Criteria and testing procedures for Category III combination products (for oral use unless otherwise specified).) The Panel has further determined that any combination product containing more than two active ingredients from the same pharmacologic group (e.g., three antihistamines) is irrational since there seems to be no reason to expect a possible benefit from the combination, and is therefore classified by this Panel as a Category II combination.

5. *Combining of active ingredients not reviewed by the Panel from the same or different pharmacologic group.* Many CCABA preparations contain active ingredients that have not been reviewed by this Panel because they are ingredients that have been or currently are being reviewed by other OTC panels. These ingredients include acetaminophen, aspirin, benzocaine, caffeine, quinine sulfate and salicylamide. Claims such as "temporarily relieves minor sore throat pain," or "For temporary relief of headache, aches, pains and fever due to colds" are examples of the labeling commonly found on CCABA preparations containing these ingredients. Such claims do not directly relate to the active ingredients reviewed by this Panel. The Panel has reviewed, for example, antitussives and the corresponding labeling claims for cough. However, the Panel has not reviewed analgesics and/or antipyretics for the labeling claims of pain and fever.

The Panel has evaluated the active ingredients in combination products submitted for review from the standpoint of their safe and effective use as cold, cough, allergy, bronchodilator and antiasthmatic products. Active ingredients included for concurrent symptoms, e.g., an analgesic for pain, have been reviewed only for their rational use in such combination products. The determination as to the safety and effectiveness of individual analgesics, for example, remains with the OTC Internal Analgesic Panel. The following are the Panel's conclusions as to the appropriateness of such combinations:

a. *Combination products containing vitamins.* The Panel is cognizant of the popular use of vitamin C (ascorbic acid) for the prevention or treatment of the "common cold." The Panel has reviewed the available data for the ingredient as a single entity and finds that the data are insufficient to permit final classification as safe and effective for OTC use in the prevention or treatment of the cold. The Panel has discussed the safety and effectiveness of vitamins including vitamin C as claimed active ingredients elsewhere in this document. (See part IX. paragraph B.1.b. below—Vitamins used alone or in combination CCABA products with labeling claims for the prevention or treatment of the "common cold.") and (See part IX. paragraph B.2.b. below—Ascorbic acid (vitamin C).) The Panel has also discussed the labeling of these claimed active ingredients elsewhere in this document. (See part IX. paragraph B.1.b. below—Vitamins used alone or in combination CCABA products with labeling claims for the prevention or treatment of the "common cold.") and (See part IX. paragraph B.2.b. below—Ascorbic acid (vitamin C).)

The Panel found no study which demonstrated that vitamin C is unequivocally effective for the prevention or treatment of the "common cold" although some data tended to favor effectiveness for treatment of cold symptoms. Since no conclusive data on the dose or dosage schedule are available on vitamin C used alone or in combination products with other ingredients for prevention or treatment of the cold, the Panel is unable to propose adequate labeling with a dosage regimen and has therefore classified such labeling as Category II. In summary, the Panel has reviewed vitamin C and has classified the "ingredient" as Category III and any "labeling" for the prevention or treatment of the cold as Category II.

With regard to combination products, the Panel further notes that the use of vitamins in CCABA combination products for the prevention of colds is irrational since the other ingredients in these products should only be used when the symptoms of the "common cold" are present. It is difficult for the Panel to rationalize the use of vitamin C or any other vitamin for the treatment of the "common cold" in combination products which are to be used only for a short duration while symptoms persist. It would be illogical for a consumer to take a cold combination product to prevent a cold. The Panel has therefore placed the labeling claims of combination products containing vitamins including vitamin C for prevention of the "common cold" in Category II.

b. *Combination products containing antihistamines with sleep-aid claims.* Antihistamines are primarily useful for relief of allergic disorders but secondarily act centrally to produce sedation or sleep. The Panel has discussed the safety and effectiveness of antihistamines elsewhere in this document. (See part VII. below—Antihistamines.) The Panel has established a safe and effective dosage range for certain antihistamines when used to treat symptoms of running nose, sneezing, itching nose or throat and watery eyes. The Panel has recommended that the labeling for these ingredients contain the warning, "May cause drowsiness".

The Panel notes that CCABA combination products are currently available for use at bedtime and promoted for such various claims as "for restful sleep". The Panel recognizes that if the symptoms of cough and cold are adequately treated, there is a greater likelihood of normal sleep. However, the duration of drug effects from "nighttime cold preparations" which are recommended to be taken once at bedtime is not fully documented.

The Panel is unable to make a final determination as to safe and effective use of an antihistamine or other agent when used as a sleep-aid in CCABA preparations. It is obvious an antihistamine may have several activities, e.g., antitussive, antihistamine, or sedative activity depending upon the dosage level used. The Panel has therefore placed sedation claims associated with CCABA combination products containing an antihistamine in Category III. The Panel further concludes that the combining of an additional antihistamine in a CCABA combination product for the exclusive purpose of sedation is irrational. Therefore, the Panel classifies such combinations as Category II.

c. *Combination products containing analgesics and antipyretics.* Many currently marketed combination products contain analgesics and antipyretics for treatment of concurrent symptoms of headaches, muscular aches, pains and fever which accompany colds. The Panel finds these claims to be acceptable and rational. Therefore, where not expressly prohibited, a generally recognized as safe and effective analgesic and/or antipyretic may be combined with the Category I ingredients reviewed by the Panel. Certain combinations that are contraindicated and placed in Category II are summarized below. (See part II. paragraph C.9. below—Criteria for Category II combination products (for oral use unless otherwise specified).)

d. *Combination products containing local anesthetics or other agents with*

claims for relief of sore throat. The symptoms of sore throat often accompany cough and the "common cold." It is usually a simple irritation aggravated by breathing through the mouth. The Panel has referred the evaluation of the safety and effectiveness of individual ingredients and labeling claims for sore throat to the OTC Oral Cavity Panel. The Panel believes that combination products containing safe and effective agents to relieve minor throat irritation are rational. The Panel has therefore placed combinations containing local anesthetics with other Category I CCABA agents in Category I. The Panel recommends that labeling contain adequate warnings against use when persistent or chronic sore throat is present and is accompanied by fever or other symptoms. (See part II. paragraph F. below—Deferral of "Sore Throat" Claim.)

The Panel recognizes that most sore throat remedies are applied topically while other symptoms of the cold are usually treated internally through oral ingestion. As an example, a throat lozenge containing a local anesthetic (benzocaine) and an antitussive (dextromethorphan) produces two pharmacologic activities. The lozenge releases benzocaine locally in the oral cavity whereas the dextromethorphan is ingested for a systemic action.

e. *Combination products containing correctives (stimulants and sedatives).* The Panel is aware that caffeine is included in some CCABA preparations with claims such as "for relief without drowsiness". Caffeine is also sometimes added to a combination product with no reference in the labeling as to its pharmacologic activity. The Panel presumes that the rationale for the inclusion of caffeine in such combinations is to reduce the sedating side effects of antihistamines.

While the Panel agrees with the rationale for caffeine serving as a "stimulant corrective," combinations containing it are placed in Category III until such "corrective" pharmacological action can be proven. This activity of caffeine should be identified on the label as "an ingredient added to counteract drowsiness caused by other drugs in this product." Where caffeine is added only as a corrective, labeling claims such as "for relief without drowsiness" are unjustified and are therefore misleading. The Panel has classified such labeling claims as Category II.

The Panel believes that combining Category I CCABA ingredients with a stimulant such as caffeine at a fully effective dose (not as a corrective) is irrational since the Panel is unaware of a significant target population having a need for CCABA ingredients and a stimulant. Accordingly, the Panel places combinations of CCABA ingredients combined with stimulants at effective dosage levels in Category II.

In addition, sympathomimetic drugs and theophyllines may cause central nervous system stimulation in some patients. To counteract this effect the Panel presumes that phenobarbital has been added to some combinations as a "sedative corrective" rather than as an active ingredient. While the Panel agrees with the rationale for phenobarbital serving as a "sedative corrective," combinations containing it are placed in Category III until such "corrective" pharmacologic action can be proven. (See part IX. paragraph B.2.d. below—Phenobarbital.) This activity of phenobarbital should be identified on the label as "an ingredient added to counteract nervousness caused by other drugs in this product." The Panel has included in this document a protocol designed to evaluate the effectiveness of phenobarbital under the above circumstances to show whether it has an additional beneficial or adverse effect on bronchospasm. (See part IX. paragraph B.2.d.(5) below—Evaluation.)

6. *Labeling of active ingredients.* As discussed above, the Panel has determined that each claimed active ingredient in a combination product must make a contribution to the claimed effect(s). (See part II. paragraph C.1. above—General combination policy.) Based upon this determination, the Panel concludes that combination products must be labeled to reflect all of the proven pharmacologic activities of each active ingredient in the combination. If a single ingredient has several activities, these should all be identified in the labeling consistent with the activities found at the recommended dosage for the product.

The Panel recommends that the labeling of a combination product containing active ingredients for treatment of concurrent symptoms emphasize the use of the product only when all such symptoms are present. The consumer should be adequately informed through the labeling of the therapeutic capabilities of the product. If, for example, only the symptom of running nose is present, a single ingredient rather than a combination product would be the rational therapy. Labeling should therefore fully reflect the activities of all active ingredients at the dosage recommended so that a consumer may select an appropriate product for relief of concurrent symptoms. If a product contains an active ingredient for which no labeling claim is made, it is clearly misleading to the consumer.

7. *Marketing experience for cold, cough, allergy, bronchodilator and antiasthmatic combination products.* The Panel recognizes the extensive marketing history of CCABA preparations. The drug industry presented data to the Panel summarizing consumer complaint information obtained from a survey of 32 pharmaceutical manufacturers (Ref. 2). A total of 117 combination CCABA products representing over 4 billion package units were included in the survey. The products were combinations of 83 ingredients representing 9 pharmacologic groups (nasal decongestants, antitussives, expectorants, antihistamines, anticholinergics, bronchodilators, analgesics, sedatives and stimulants). Inactive ingredients such as glycine and alcohol were also included in the data presented.

The drug industry reported to the Panel that the overall number of consumer complaints in the survey, in terms of either adverse reactions and/or ineffectiveness was less than one complaint per one million packages sold. However, from the survey data the Panel is unable to determine whether the information on adverse reactions was gathered during the entire period for which marketing data were reported for the products. The drug industry acknowledged that not every consumer complaint is well-founded or attributable to the drug product. In addition, not every consumer who fails to receive relief or experiences side effects registers complaints with the drug manufacturer.

The Panel has considered the marketing data submitted. The Panel finds that of the 83 ingredients included in the survey, only 11 ingredients have been classified by the Panel as Category I whereas 27 have been classified as Category III. Only one of the ingredients, belladonna alkaloids, has been classified as Category II when used by inhalation in the treatment of asthma. The remaining ingredients were not submitted for review to the Panel, pursuant to the call for data published in the FEDERAL REGISTER of August 9, 1972 (37 FR 16029), and therefore were not considered by the Panel. Several of these ingredients are currently available only by prescription while others are inactive ingredients. The actual quantities of active ingredients contained in the products and the amounts actually consumed by consumers were not included in the survey data and can only be estimated.

It would appear from the data that there is a low incidence of obvious adverse reactions which the consumer can attribute to the drug product. Since the quantities of drug administered in the surveyed products are not known, the Panel has reviewed the quantities of active ingredients contained in the marketed products submitted for review to the Panel. (See part I. paragraph A. above—Submissions by Firms.) The Panel presumes that the quantities of active ingredients contained in these products are generally representative of the products contained in the survey. The Panel concludes that while marketing data are limited and difficult to interpret they tend to support the safe use of combinations of active ingredients reviewed by the Panel.

The fact that over 4 billion packages of the 117 combination products have been sold would tend to indicate that consumers perceive a need for such drugs. It is obvious that consumers believe these products useful, to account for the many sales, but the extent to which this belief by the consumer is established by advertising rather than by a need perceived independently of advertising cannot be determined by the Panel. In addition, belief in the usefulness of a product may be related to a placebo response and also to the fact that a self-limiting illness is being treated.

Regarding effectiveness, the Panel has applied the OTC Drug Review Regulation (21 CFR 330.10(a)(4)(ii)) which provides, that as a source of corroboration for proof of effectiveness, the reports of significant human experience during

marketing are appropriate. The Panel finds the data helpful but not conclusive. The Panel believes that marketing experience, in and of itself, cannot be regarded as constituting adequate proof of effectiveness. Since the amounts of active ingredients included in the survey are not known, it is difficult for the Panel to determine the effectiveness of these combination products.

Data were contained in the survey of combinations by pharmacologic groups. For example, products with antitussives and nasal decongestants were compared to products containing antitussives, nasal decongestants and expectorants, etc. The data tend to indicate the addition of a drug from an additional pharmacologic group does not alter the complaint ratios. The Panel concludes that the data meet the criteria of the regulation (21 FR 330.10(a)(4)(ii)) and are limited but tend to support the effective use of certain combinations.

8. *Criteria for Category I combination products (for oral use unless otherwise specified).* Based upon an evaluation of the drug combinations submitted to the Panel for review, the following criteria have been established:

a. *Criterion.* Each claimed active ingredient and its labeling in a combination must be generally recognized as safe and effective (Category I) and each active ingredient must be combined within the established effective dosage range as set forth elsewhere in this document.

b. *Criterion.* Products containing one active ingredient from each pharmacologic group in the combinations identified below are classified as Category I combination products, provided the active ingredients and their labeling are generally recognized as safe and effective (Category I) and such ingredients are present in amounts within the effective dosage range.

(1) Combinations containing an analgesic-antipyretic and an antihistamine.

(2) Combinations containing an analgesic-antipyretic and a nasal decongestant.

(3) Combinations containing an analgesic-antipyretic, a nasal decongestant and an antihistamine.

(4) Combinations containing an antihistamine and an antitussive provided the product is labeled *"Caution:* May cause marked drowsiness." The labeling term "marked" relating to the warning statement may be removed if adequate data are supplied to the Food and Drug Administration to demonstrate that the combination product does not cause a significant increase in drowsiness as compared with each ingredient when tested alone.

(5) Combinations containing an antihistamine and a nasal decongestant.

(6) Combinations containing an antihistamine, an antitussive and a nasal decongestant.

(7) Combinations containing an antitussive and an expectorant provided the product is labeled only for nonproductive cough. Expectorants are expected to have their major usefulness in the irritative nonproductive cough as well as those coughs productive of scanty amounts of thick, sticky secretions. Antitussives suppress the act of coughing and may promote retention of some mucous secretions and thereby coat inflamed bronchial membrane linings.

(8) Combinations containing an antitussive and a nasal decongestant.

(9) Combinations containing an antitussive and a local anesthetic or local analgesic-antipyretic provided the product is available only as a lozenge.

(10) Combinations containing an antitussive, an expectorant and a nasal decongestant provided the antitussive and expectorant ingredients in the product are labeled only for nonproductive cough. Expectorants are expected to have their major usefulness in the irritative nonproductive cough as well as those coughs productive of scanty amounts of thick, sticky secretions. Antitussives suppress the act of coughing and may promote retention of some mucous secretions and thereby coat inflamed bronchial membrane linings.

(11) Combinations containing an oral bronchodilator and an expectorant provided the product is labeled only for cough associated with asthma.

(12) Combinations containing an oral bronchodilator (sympathomimetic) and an oral bronchodilator (theophylline).

(13) Combinations containing an expectorant and a nasal decongestant.

(14) Combinations containing a nasal decongestant and a local anesthetic or local analgesic-antipyretic provided the product is available only as a lozenge.

9. *Criteria for Category II combination products (for oral use unless otherwise specified).* Based upon an evaluation of the drug combinations submitted to the Panel for review, the following criteria have been established:

a. *Criterion.* A combination is Category II if a Category II ingredient or labeling is present in the combination product.

b. *Criterion.* A combination product containing Category I ingredients from different pharmacologic groups is classified as Category II if it includes any ingredient(s) at less than the minimum effective dosage established by the Panel unless the ingredient(s) are being used to treat the same symptom. (See Part II. paragraph C. 10.b.(1) below—Category III Combination.)

c. *Criterion.* If a product contains an active ingredient or labeling that has not been reviewed by this or other OTC Advisory Review Panels, such ingredient or labeling is classified by this Panel as Category II.

d. *Criterion.* A combination product is classified as Category II if it includes more than two active ingredients from the same pharmacologic group.

e. *Criterion.* Combinations of active ingredients and labeling which have been determined by the Panel to be unsafe or irrational and classified as Category II are as follows:

(1) Combinations containing an analgesic-antipyretic and a bronchodilator. This combination contains an analgesic for the symptomatic treatment of fever or muscular aches, etc., associated with the "common cold" and contains a bronchodilator with a claim for the treatment of symptoms of asthma. The Panel concludes that if an individual with a cold needs relief of asthma, he should take a bronchodilator separately since there may be a more frequent need of this drug than for the other ingredients contained in the preparation. In addition, the Panel further concludes that a bronchodilator should only be labeled for use in patients with asthma and that the addition of an analgesic is irrational. The Panel believes that for treatment of concurrent symptoms where an asthmatic requires an analgesic or antipyretic, he should take such drugs separately because the dosage and need for each of the ingredients varies with the likelihood that the bronchodilator is more frequently required.

(2) Combinations containing an anticholinergic and an expectorant. This combination is irrational because an expectorant promotes the production of secretions whereas the anticholinergic produces an opposite effect, i.e., antisecretory action.

(3) Combinations containing an antihistamine and an expectorant. This combination is irrational because an expectorant promotes the production of secretions whereas the anticholinergic activity of an antihistamine produces an opposite effect, i.e., anti-secretory action.

(4) Combinations containing a bronchodilator and an anticholinergic. This combination is irrational because the anti-secretory action of the anticholinergic may produce thickened bronchial secretions which may cause further obstruction of the airways in individuals with asthma.

(5) Combinations containing a bronchodilator and an antihistamine. This combination is irrational because the anticholinergic effect, i.e., anti-secretory action, of antihistamines may produce thickened bronchial secretions which may cause further obstruction of the airways in individuals with asthma.

(6) Combinations containing an oral bronchodilator and an antitussive when the product is labeled only for cough associated with asthma. This combination is irrational because the antitussive suppresses cough and the cough reflex is essential in asthma to maintain an open airway by clearing the respiratory passages of excessive secretions.

(7) Combinations containing an antitussive and an antihistamine if the antitussive is also generally recognized as safe and effective as an antihistamine. This combination is not safe because the antihistaminic side effects of the antitussive may combine with the side effects of the antihistamine.

(8) Combinations containing an antihistamine and an antitussive if the antihistamine is also generally recognized as safe and effective as an antitussive. This combination is not safe because the antitussive side effects of the antihistamine may combine with the side effects of the antitussive.

f. *Criterion.* Combination products containing any vitamins, e.g., vitamin C, with labeling claims which represent or

suggest the product for the prevention or treatment of the "common cold". (See part II. paragraph C.5.a. above—Combination products containing vitamins.)

g. *Criterion.* Combination products containing a stimulant, e.g., caffeine, at a fully effective level (not as a "corrective"). (See part II. paragraph C.5.e. above—Combination products containing correctives (stimulants and sedatives).)

h. *Criterion.* Combination products containing more than one antihistamine in which an additional antihistamine is added for the exclusive purpose of sedation and the product contains labeling which represents or suggests the additional antihistamine as a "sleep-aid." (See part II. paragraph C.5.b. above—Combination products containing antihistamines with sleep-aid claims.)

10. *Criteria and testing procedures for Category III combination products (for oral use unless otherwise specified).* Based upon an evaluation of the drug combinations submitted to the Panel for review the following criteria and corresponding testing procedures are recommended:

a. *Criterion.* (1) *Category III combination.* If a Category III ingredient or labeling is present in a combination product containing no Category II ingredient or labeling, the combination is classified as Category III.

(2) *Category III testing procedure.* The Category III ingredient (or ingredients) for the labeling claims (symptom(s)) must be tested in accordance with the evaluation protocol specified for that particular pharmacologic group. The appropriate protocol(s) under the heading "Data Required for Evaluation" are identified elsewhere in this document for each respective pharmacologic group. If when tested alone the Category III ingredient (or ingredients) can be shown to be safe and effective in accordance with the standards for evaluation established in the protocol(s), it then qualifies for Category I status. The combination will then contain only Category I ingredients and will be considered Category I without further testing provided the combination is identified above. (See part II. paragraph C.8.b. above—Criterion.)

b. *Criterion.* (1) *Category III combination.* If two or more ingredient(s) are being used to treat the same symptom (labeling claim), a combination product is classified as Category III even if it contains Category I ingredients from different pharmacologic groups when any ingredient(s) is present at less than the minimum effective dosage established by the Panel.

(2) *Category III testing procedure.* An acceptable test procedure will be one in which the combination, each of the individual ingredients in the minimum effective dosage, and each of the individual ingredients in the less than the minimum effective dosage used in the combination, and a placebo are evaluated, all in the same study, against the relevant symptom (labeling claim). In this way, comparisons of safety and effectiveness can be made directly between the combination, the individual ingredients and the placebo. The appropriate protocol(s) under the heading "Data Required for Evaluation" are identified elsewhere in this document for each respective pharmacologic group. Each individual ingredient which is in less than the minimum effective dosage should demonstrate a contribution, but not necessarily a significant effect, against the relevant symptom when compared to placebo. It is very difficult to develop a generally applicable definition of a "contribution." Each ingredient and the symptom that it should affect must be analyzed individually as to the effect on the patient population in which it is being used. For an ingredient to be judged as contributing to the alleviation of the relevant symptom, the Panel suggests that the drug effect should demonstrate a 10 percent or greater difference from placebo.

For a combination of Category I ingredients from different pharmacologic groups used to treat the same symptom and in which at least one of the ingredients is in less than the minimum effective dosage, to be classified as a Category I combination, the relative incidence of side effects and/or other untoward effects of the combination should not be significantly greater than those of any individual ingredient in that combination alone in the minimum effective dosage. In addition, the combination must exert a significant effect against the relevant symptom which is not less than any one of the ingredients when tested alone in the minimum effective dosage. The justification for these requirements is that such a combination should not compromise effectiveness nor should it pose a greater risk of side effects than is associated with an ingredient alone in its minimum effective dosage.

c. *Criterion.* (1) *Category III combination.* A combination product is classified as Category III if it includes two Category I ingredients from the same pharmacologic group.

(2) *Category III testing procedure.* An acceptable test procedure will be one in which the combination, each of the individual ingredients, at its minimum effective dosage, and a placebo are evaluated, all in the same study, against the relevant symptom (labeling claim). In this way, comparisons of safety and effectiveness can be made directly between the combination, the individual active ingredients from the same pharmacologic group at its minimum effective dosage and the placebo. The appropriate protocol(s) under the heading "Data Required for Evaluation" are identified elsewhere in this document for each respective pharmacologic group.

For a combination of two Category I ingredients from the same pharmacologic group to be classified as a Category I combination, the relative incidence of side effects and/or other untoward effects of the combination should not be significantly greater than those of either individual ingredient alone at its minimum effective dosage. In addition, the combination must exert a significant effect against the relevant symptom(s) which is not less than either one of the ingredients when tested alone at its minimum effective dosage. The justification for these requirements is that such a combination should not compromise effectiveness nor should it pose greater risk of side effects than is associated with an individual ingredient alone.

d. *Criterion.* (1) *Category III combination.* A combination product containing two Category I ingredients from the same pharmacologic group is classified as Category III if it includes either or both ingredient(s) at less than the minimum effective dosage established by the Panel.

(2) *Category III testing procedure.* An acceptable test procedure will be one in which the combination, each of the individual ingredients in the minimum effective dosage, and each of the individual ingredients in the less than the minimum effective dosage used in the combination, and a placebo are evaluated, all in the same study, against the relevant symptom. In this way, comparisons of safety and effectiveness can be made directly between the combination, the individual active ingredients from the same pharmacologic group and the placebo. The appropriate protocol(s) under the heading "Data Required for Evaluation" is identified elsewhere in this document for each respective pharmacologic group. Each individual ingredient which is in less than the minimum effective dosage should demonstrate a contribution, but not necessarily a significant effect, against the relevant symptom when compared to placebo. It is very difficult to develop a generally applicable definition of a "contribution." Each ingredient and the symptom that it should affect must be analyzed individually as to the effect on the patient population in which it is being used. For an ingredient to be judged as contributing to the alleviation of the relevant symptom, the Panel suggests that the drug effect should demonstrate a 10 percent or greater difference from placebo.

For a combination of two Category I ingredients from the same pharmacologic group to be classified as a Category I combination, the relative incidence of side effects and/or other untoward effects of the combination should not be significantly greater than those of either individual ingredient alone in the minimum effective dosage. In addition, the combination must exert a significant effect against the relevant symptom which is not less than either one of the ingredients when tested alone in the minimum effective dosage. The justification for these requirements is that such a combination should not compromise effectiveness nor should it pose greater risk of side effects than is associated with an individual ingredient alone in the minimum effective dosage.

e. *Criterion.* (1) *Category III combination.* Combinations of active ingredients for which the available safety data are insufficient for the Panel to make a final

determination and are classified as Category III: (i) Combinations containing atropine and an oral nasal decongestant. Additional studies are necessary to assess the potential additive central nervous system stimulant side effects.

(ii) Combinations containing an antihistamine and an anticholinergic. Additional studies are necessary to assess the nature and extent of additive anticholinergic side effects.

(2) *Category III testing procedure.* An acceptable test procedure will be one in which the combination and a placebo are evaluated in suitable subjects so that comparisons can be made of the particular side effect(s) of concern which are specified above. In addition, data on the relative incidence and intensity of those side effects must be available for the individual active ingredients in the same dosage as in the combination either evaluated in the same study as above, or evaluated in a separate study using a comparable test protocol. The appropriate protocol(s) under the heading "Data Required for Evaluation" are identified elsewhere in this document for each respective pharmacologic group.

If the relative incidence and intensity of the side effect(s) of the combination are increased to a degree which prevents its safe use as an OTC product, it will be classified as a Category II combination for those dosages. If the relative incidence and intensity of side effect(s) are significantly greater than with either ingredient administered alone but not to a degree to prevent its safe OTC use, a suitable warning regarding potential for that side effect should be specified in the labeling for the combination product. If the relative incidence and/or intensity of side effect(s) with the combination are not significantly greater than with either ingredient administered alone, no warnings other than the standard Category I warnings for those ingredients are needed on the label.

f. *Criterion.* (1) *Category III combination.* Combinations of active ingredients for which the available effectiveness data are insufficient for the Panel to make a final determination or for which there is no rationale for use and are classified as Category III are as follows: (i) Combinations containing a nasal decongestant and an antihistimine administered topically as a spray or drops. Additional studies are necessary to assess the contribution of the antihistamine administered by the topical route since there are inadequate studies demonstrating the effectiveness of the antihistamines topically in such combinations.

(ii) Combination products containing an antitussive and a bronchodilator used as an antitussive provided the product is labeled only for cough not associated with asthma. Additional studies are necessary to assess the antitussive effects of a bronchodilator in combination with an antitussive in reducing cough.

(iii) Combination products containing an expectorant and a bronchodilator used as an antitussive provided the product is labeled only for cough not associated with asthma. Additional studies are necessary to assess the antitussive effects of a bronchodilator in combination with an expectorant in reducing cough.

(iv) Combination products containing an antitussive and an expectorant provided the product is labeled only for productive cough. Additional studies are necessary to assess the combined effects of an antitussive and an expectorant in the presence of excessive or more fluid bronchial secretions.

(v) Combination products containing an antitussive, an expectorant and a nasal decongestant provided the antitussive and expectorant ingredients in the product are labeled only for productive cough. Additional studies are necessary to assess the combined effects of an antitussive and an expectorant in the presence of excessive or more fluid bronchial secretions.

(2) *Category III testing procedure.* An acceptable test procedure will be one in which the combination, each individual ingredient, and a placebo are evaluated against the relevant symptoms either in the same study or in separate studies using comparable test protocols. The appropriate protocol(s) under the heading "Data Required for Evaluation" is identified elsewhere in this document for each respective pharmacologic group. In this way, comparisons of effectiveness can be made between the combination, the individual active ingredients and the placebo by that route of administration. When tested alone by that route of administration, each individual ingredient should demonstrate a significant effect against the relevant symptom when compared to placebo.

For the combination of Category I ingredients from different pharmacologic groups to be a Category I combination by that route of administration, the combination must also exert a significant effect against each of the relevant symptoms when compared with the placebo.

g. *Criterion.* (1) *Category III combination.* Combination products containing an active ingredient specifically intended to counteract a side effect of other ingredients in the product, i.e., a "corrective", for which the available data are insufficient for the Panel to make a final determination, are classified as Category III.

(2) *Category III testing procedure.* An acceptable test procedure will be one in which the combination with and without the corrective is evaluated to assess the effectiveness of the corrective to significantly decrease the incidence and/or intensity of the undesirable side effect, and to assess the safety of this combination.

h. *Criterion.* (1) *Category III combination.* Combination products containing an antihistamine with a sleep-aid claim for which data are insufficient for the Panel to make a final determination and are classified as Category III.

(2) *Category III testing procedure.* If a sleep-aid effect is claimed for the antihistamine, the Panel recommends a testing protocol in conformance with requirements specified by the OTC sedative, tranquilizer and sleep-aid drug products Panel as published in the FEDERAL REGISTER of December 8, 1975 (40 FR 57292).

i. *Criterion.* (1) *Category III combination.* Combination products containing several claimed active ingredients which are mixtures of volatile substances with overlapping pharmacologic activities for which a minimum effective dosage cannot be established for one or more of the ingredients when tested alone are classified as Category III.

(2) *Category III testing procedure.* An acceptable test procedure will be one in which the combination, each of the individual ingredients in the dosage used in the combination, and a placebo must be evaluated against the relevant symptom (labeling claim), either in the same study, or in separate studies using comparable test protocols. The appropriate protocol(s) under the heading "Data Required for Evaluation" are identified elsewhere in this document for each respective pharmacologic group. When tested alone, each individual ingredient should demonstrate a contribution, but not necessarily a significant effect, against the relevant symptom when compared to placebo. It is very difficult to develop a generally applicable definition of a "contribution." Each ingredient and the symptom that it should affect must be analyzed individually as to the effect on the patient population in which it is being used. For an ingredient to be judged as contributing to the alleviation of the relevant symptom, the Panel suggests that the drug effect should demonstrate a 10 percent or greater difference from placebo.

For the combination of these ingredients to be classified as Category I, it must exert a significant effect against the relevant symptom when compared to placebo meeting the standards of evaluation set forth for that pharmacologic group. Furthermore, the combination product must be judged safe for OTC use as evaluated by the incidence and/or intensity of side effects and/or other untoward effects.

j. *Criterion.* (1) *Category III combination.* There is lack of data on a suitable target population with concurrent symptoms of sufficient duration to justify combination products containing four or more different pharmacologic groups. Therefore, the Panel classifies combination products containing four or more different pharmacologic groups as Category III. Examples of such combinations are as follows:

(i) Combinations containing an analgesic-antipyretic, an antitussive, an expectorant and a nasal decongestant.

(ii) Combinations containing an analgesic-antipyretic, an antitussive, an antihistamine and a nasal decongestant.

(2) *Category III testing procedure.* Before such combinations may be classified as Category I, a significant target population requiring such a combination for the treatment of concurrent symptoms of sufficient duration and severity must be identified by appropriate epidemiological studies. If a suitable target population is

found such combinations may be classified as Category I.

REFERENCES

(1) "AMA Drug Evaluations," 2d Ed., American Medical Association, Chicago, pp. 492–503, 1973.

(2) OTC Volume 040287.[1]

(3) Cohen, B. M., "Sympathomimetic/Xanthine Broncholysis in Obstructive Ventilatory Disorders," *International Journal of Clinical Pharmacology*, 9:6–15, 1974.

D. STATEMENT ON CATEGORY III TESTING PROCEDURES

1. *Comments on study design.* The Panel has agreed that the protocols recommended in this document for the studies required to bring a Category III drug into Category I are in keeping with the present state of the art and do not preclude the use of any advances or improved technology in the future.

Experimental design should take into account the need to include a sufficient number of subjects or trials so as to provide meaningful conclusions which can be supported by appropriate statistical analysis. The selection of appropriate subjects or patients can be of major importance when the effect of a drug in a specific illness or symptom is under study.

A role for bias is assumed in all situations wherein the subject, the observer or both make a judgment as to the nature of magnitude of a response. Biological factors also contribute to variation in response between individuals in a given study sample. Although bias and biological variation cannot be eliminated, their effect on the outcome of an experiment can be avoided or minimized by adopting a "double-blind, placebo-controlled" or other suitably blinded design. In such a design, one group of subjects receives a placebo or dummy preparation so that the response unmodified by drug under test can be established. Neither the subjects nor the observer should be able to detect the identity of the preparations under test. This requires that the test and placebo preparations be indistinguishable in regard to taste, color and shape except in the case of preparations containing volatile substances where it will be impossible to make the active ingredients indistinguishable from the placebo.

It is often desirable to include a standard drug (a drug used as a positive control known to exert a significant effect against the relevant symptom(s) being tested) with which the unknown can be compared. Finally the inclusion of two or more dose levels of the drug under test may be desirable in order to provide an estimate of an effective therapeutic dose range free from undesirable side effects. If a crossover design is utilized, i.e., each subject serves as his own control, the sequence in which the placebo, standard and test drugs are administered should be randomized and a sufficient "washout period" between tests should be permitted.

Wherever possible, objective measurements should be made in perference to subjective judgments. However, such measurements should be relevant to the symptom or symptom complex for which the drug under test is to be used.

2. *Testing period provided for Category III conditions.* The Panel concludes that the conditions excluded from the monograph on the basis of the Panel's determination that the available data are insufficient (Category III) to classify such conditions either as Category I—generally recognized as safe and effective and not misbranded, or as Category II—not being generally recognized as safe and effective, or would result in misbranding be permitted to remain in use for the period of time specified below after the date of publication of the final monograph in the FEDERAL REGISTER, if the manufacturer or distributor of any such drug utilizing such conditions in the interim conducts tests and studies adequate and appropriate to satisfy the questions raised with respect to the particular condition by the Panel.

The Panel has established the following specific time limitations for testing based upon the applicable pharmacologic group:

	Time provided for testing (years)
Pharmacologic group:	
Anticholinergic	3
Antihistamine	3
Antitussive	4
Bronchodilator sympathomimetic	3
Bronchodilator theophylline	3
Expectorant	5
Nasal decongestant	3

The Panel believes that testing for bronchodilators, antihistamines, anticholinergics and nasal decongestants can be completed within 3 years. The techniques for testing are all well-established and are discussed in the relevant sections of the document below. The Panel feels that 1 year is necessary for the development of protocols with 2 years provided for the actual testing. Clinical testing should start within 6 months of publication of the final monograph.

The techniques for testing antitussives involve cough counting. At present, there are relatively few laboratories available to do this work, and the techniques are very time-consuming. Because of these factors, 4 years have been provided as the time limitation. Clinical testing should start within 1 year of the publication of the final monograph.

The Panel recognizes that the evaluation of expectorants is difficult and there is no completely accepted technique available for the assessment of this pharmacologic group of drugs. It seems likely that new techniques will have to be developed for effective testing of these substances. Because of the need for developmental technical work, the time limitation is placed at 5 years. Clinical testing should start within 18 months of the publication of the final monograph.

The Panel concludes that for Category III combination drug products containing more than one pharmacologic group, the time established for testing shall be determined by the pharmacologic group having the longest period provided for testing. (See part II. paragraph C.10 above—Criteria and testing procedures for Category III combination products (for oral use unless otherwise specified).)

In addition to establishing time limitations of testing for specific pharmacologic groups, the Panel has established the following periods for testing of other Category III conditions:

	Time provided for testing (years)
Category III condition:	
Antihistamines with sleep-aid claims	3
Caffeine (stimulant corrective)	2
Phenobarbital (sedative corrective)	2
Timed-release drug formulations	4
Vitamin C (ascorbic acid)	3

The Panel recognizes that CCABA combination products are available for use at bedtime and promoted for such various claims as "for restful sleep." The Panel has discussed sleep-aid claims elsewhere in this document (See part II. paragraph C.5.b. above—Combination products containing antihistamines with sleep-aid claims).

The Panel is unable to make a final determination as to safe and effective use of antihistamines or other agents as sleep-aids in CCABA preparations. The Panel has therefore placed sedation claims associated with CCABA combination products containing antihistamines in Category III and has provided 3 years for testing and documentation of such claims.

The Panel is aware that caffeine is included in some CCABA preparations with claims such as "for relief without drowsiness". Caffeine is also contained in combination products with no reference in the labeling as to its pharmacologic activity. The Panel presumes that the rationale for the inclusion of caffeine in such combinations is to reduce the sedating side effects of antihistamines. The Panel has discussed the use of "stimulant correctives" elsewhere in this document. (See part II. paragraph C.5.e. above—Combination products containing correctives (stimulants and sedatives).) The Panel agrees with the rationale for caffeine serving as a "stimulant corrective" but combinations containing it are placed in Category III until such "corrective" pharmacological action can be proven. The Panel has provided 2 years for testing and documentation of such claims.

Timed-release drug formulations have been reviewed elsewhere in this document. (See part II. paragraph E. below—Effect of Timed-Release Formulations on Effectiveness and Safety of OTC Drug

[1] Cited OTC Volumes refer to the submissions made by interested persons pursuant to the call for data notice published in the FEDERAL REGISTER of August 9, 1972 (37 FR 16029). The volumes are on file in the office of the Hearing Clerk, Food and Drug Administration, Room 4–65, 5600 Fishers Lane, Rockville, MD 20852.

Products.) The Panel has provided 4 years for the development of suitable tests for the standardization of all OTC timed-release CCABA products.

Vitamin C (ascorbic acid) has been reviewed elsewhere in this document. (See part IX. paragraph B.1.b. below—Vitamins used alone or in combination CCABA products with labeling claims for the prevention or treatment of the "common cold" and part IX. paragraph B.2.b. below—Ascorbic acid (vitamin C).)

The Panel concludes that the effectiveness of vitamin C in the prevention or treatment of the "cold" has not been established and has classified the ingredient as Category III with 3 years provided for testing. However, all labeling claims for the ingredient for the prevention or treatment of the "cold" are classified as Category II.

Phenobarbital has been reviewed elsewhere in this document. (See part II. paragraph C.5.e. above — Combination products containing correctives (stimulants and sedatives) and part IX. paragraph B.2.d. below—Phenobarbital.) Several products used in the treatment of the symptoms of asthma contain drugs which stimulate the central nervous system in some patients. The Panel presumes that phenobarbital is included to counteract these effects and is therefore a "sedative corrective" rather than an active ingredient. The Panel agrees with the rationale for phenobarbital serving as a "sedative corrective" but has classified such combinations as Category III until such "corrective" action is proven. The Panel has provided 2 years for testing and documentation of such claims.

E. EFFECT OF TIMED-RELEASE FORMULATIONS ON EFFECTIVENESS AND SAFETY OF OTC DRUG PRODUCTS

1. *Introduction.* The oral route is the most common method of administration for OTC cold, cough, allergy, bronchodilator and antiasthmatic products. Such products are swallowed and absorbed from the stomach and intestines. Drugs administered orally are dissolved in gastrointestinal fluids and are absorbed into the systemic circulation where they exert an action on "target" organs or receptors. Generally, this action occurs within an hour or so of ingestion of the drug and peaks, e.g., in an hour or two, but the drug action lasts for several hours, e.g., 3 to 6 hours. When the drug action begins to decline, e.g., at the end of 3 to 6 hours, it is necessary to take another dose so that the desired action will continue at a more or less constant level. Most drug studies showing safety and effectiveness have been carried out with oral dosage forms that act in this manner. There are, however, a number of OTC CCABA products that are formulated in another kind of oral dosage form called timed-release formulations. Theoretically, these products are formulated so as to dissolve in gastrointestinal fluids in a controlled manner so that small amounts will be absorbed over a longer period of time, e.g., over 3 to 6 hours rather than 1 hour, and the duration of drug action will be extended over a longer period, e.g., 8 to 12 hours rather than 3 to 6 hours.

Since the specific formulation of a product can affect its safety and effectiveness, the Panel has considered timed-release formulations of OTC products under its review. The Panel did not consider in detail each of these formulations nor evaluate the dissolution times of the specific formulation or the affect of formulation on safety and effectiveness of each individual ingredient under review when formulated in this unique manner. The Panel does recognize certain advantages and disadvantages of timed-released formulations. The Panel has reviewed the pertinent literature and selected articles regarding timed-release formulations and has set forth certain guidelines to be used in their evaluation (Refs. 1 through 9).

2. *General discussion.* To produce its characteristic effect, a drug must achieve adequate concentrations at its site of action. One important factor in determining the concentration attained is the extent and rate of drug absorption. Other factors include the amount of drug administered, its distribution within the body, binding or localization in tissues, inactivation or metabolism and excretion.

The latent period between administration of a drug and its onset of action is influenced by the route of administration, e.g., orally, topically, by inhalation, etc., and the rate of absorption and the penetration of the drug at the site of action. The duration of drug effects is determined largely by the rate of inactivation and excretion of the drug. The duration of action of the drug effect is determined by a balance between all of these factors.

The rate of absorption of oral dosage forms is dependent mainly on their dissolution rate in gastrointestinal fluids. Theoretically, slow release and sustained effects (up to 8 hours or longer) of drugs administered in oral dosage forms should be attained if such drugs are formulated so as to dissolve in gastrointestinal fluids in a controlled manner.

A number of the active ingredients reviewed by the Panel are presently formulated in repeat action or extended release dosage forms. These formulations are known by a variety of names such as sustained action, sustained release, prolonged release, controlled release, long-acting time release, etc. Repeat-action tablets periodically release complete doses of active drug to the gastrointestinal fluids. Extended-release tablets continuously release increments of the contained medication to the gastrointestinal fluids. These terms are often used interchangeably and, although technically different, are referred to in this document as timed-release formulations.

3. *Advantages.* The principle of controlled release of drugs from oral dosage units is generally accepted to provide several advantages over the conventional dosage forms that requfre a shorter time interval regimen of administration.

Among these advantages may be listed the principal ones of better patient compliance, increased patient convenience, and lower incidence and/or severity of side effects of the drugs due to elimination of the peaks in the level of drug concentration in the blood that often occur after repeated administration of traditional dosage forms.

4. *Disadvantages.* Among the disadvantages is the fact that uniformly effective preparations of time-released drugs have been difficult to achieve, in part because of technical problems associated with their manufacture, but also because the dissolution rate of these preparations in gastrointestinal fluids may be irregular and because variations in gastrointestinal acidity, gastric emptying, and intestinal motility and other physiological factors also influence drug absorption.

If reasonable uniformity of effectiveness is not achieved, for whatever reason, the dissolution rate, for example, may be so slow that no effect is achieved or, conversely, it may be so fast that the patient receives the effect of all the active drug within a short time period, resulting in an increased incidence and/or severity of side effects.

On theoretical grounds, there are a number of reasons why a given drug should not be formulated as a timed-release product. These reasons relate to the inherent nature of a specific drug. For example, a drug may have a very long half-life, i.e., it may be metabolized and eliminated from the body over a long period of time, and thus conventional dosing already provides sustained blood levels. A drug may require a very large dose before sustained action is possible and a timed-release product containing a dose sufficient for 8 or 12 hours would necessitate an inconvenient amount of drug being swallowed. Potent drugs, i.e., those having a very small difference between the effective and toxic doses, or those to which patient response is variable, necessitate individualization of dose or dosage interval, and timed-release products are designed to release the drug in a fixed pattern. Drugs that are poorly absorbed or poorly soluble are likely to be absorbed erratically, and thus the predictability of response following ingestion of a timed-released product is difficult. Since the amount of drug contained in a timed-release formulation is usually greater than in a conventional formulation, increased side effects or toxicity is possible. Variations in the patient's physiological response or a technical flaw in the formulation may result in the release of the entire amount of active drug from the formulation in a short period of time, thus producing adverse reactions.

Some drugs reviewed by the Panel are inappropriate for formulation in a timed-release product. Glyceryl guaiacolate is a drug that for effectiveness requires a relatively large dose at regular intervals. Thus, the dose of the drug required to obtain an effective action over an extended period of time, e.g., 8 to 12 hours, would be difficult to swallow. The theophyllines represent an example of a potent drug for which patient dosage should be individualized because of the drugs' variable rates of metabolism. Such

individualization of dosage is best obtained by ingestion of small doses of theophyllines at more frequent intervals than are possible with timed-release products.

All other drugs reviewed by the Panel would, on theoretical grounds, be suitable for incorporation into a timed-release product. For approval of any drug in a given type of timed-release formulation, evidence should be presented to demonstrate that blood levels or clinical effects are comparable and the incidence of side effects is not greater than that seen when compared to the preparation given in repeated, single doses (conventional dosage).

5. *Guidelines for evaluation of timed-release formulations.* Timed-release formulations generally fall into one of three major categories: Extended release—those that provide for gradual and continuous release of active substance along the gastrointestinal tract; repeated action—those that provide two or more essentially discrete release times for the active constituents, e.g., coat/core formulations; and those that combine the mechanisms of both of the foregoing kinds of formulations.

Evaluation of any type of long-acting oral formulation should accomplish two objectives. First, it should establish that the dosage form provides delayed absorption of all or part of the drug(s) as claimed in the labeling. Secondly, it should establish that the formulation delivers the claimed dosage of the drug(s) to the patient.

There are basically two major methods of evaluating these specialized dosage forms:

a. *Clinical methods.* Controlled clinical tests, aimed at measuring the magnitude and duration of either the therapeutic effect or a characteristic pharmacologic effect resulting from timed-release drug as compared to the concentration or drug activity resulting from the usual dose administered in solution or a rapidly disintegrating solid dosage form, offers an ideal way of determining the safety and effectiveness of a timed-release dosage form of a drug. Unfortunately, however, there are few objective measurements currently available that will demonstrate drug action even though there are pharmacologic responses (see other sections of this document describing evaluation protocols for clincial studies). Where such methods are available, they should be the evaluative method of choice to compare the timed-release product with suitably repeated doses of the drug in a conventional formulation. In the absence of clinical trials of timed-release preparations, blood levels and urinary excretion determinations are acceptable if these measurements can be related to pharmacologic effects.

b. *Drug absorption methods.* (1) *Blood level measurements.* Long-acting dosage forms can be evaluated by methods that measure the rate and extent to which the active ingredients are absorbed into the bloodstream. A principal way of determining this drug absorption makes use of tests in which the blood levels of the drug are measured at specified time intervals after administration of the product.

The analytical method should permit quantitative evaluation of rates of absorption, peak drug levels, and peak time and areas under blood drug-level curves. The latter are particularly useful in evaluation of time-release formulations because the area under the blood drug-level curve of such a formulation should approximate that obtained with appropriately repeated doses of a conventional oral form of the drug. Thus, for example, two experimental approaches may be considered: For coat/core formulations, the aim is to establish whether the release time of each ingredient corresponds to the labeling claim, and then to determine whether the blood-level curve obtained with the core approximates that obtained with conventional tablets; and for other timed-release formulations one can also compare blood levels with those of a conventional form of the drug when each preparation has been administered at recommended time-intervals.

Where appropriate, it is preferable to measure blood levels of the parent drug and/or its metabolites; however, urinary excretion measurements offer an alternative approach.

(2) *Urinary excretion measurements.* There are many instances where adequate reproducible methods of determining blood levels have not yet been developed. In which case, urinary analytical methods offer an alternative to blood level measurements in evaluating a timed-release oral form of a drug. Urinary excretion measurements can provide quantitative data only when the drug is excreted unchanged in the urine or when the metabolism of the drug is well understood. In utilizing measurements of urinary levels and excretion rates, the timed-release product should also be compared with suitably repeated doses of a conventional oral form of the drug. With both preparations, the urinary excretion levels and rates over the test period should be roughly similar but need not be equal.

6. *Summary.* If claims of timed-release are made, these claims must be supported by evidence as compared to usual suitably repeated doses of the drug in a conventional oral formulation. Such evidence should be obtained from studies in humans, which are based upon the measurement of a therapeutic effect or acute pharmacologic effect of the drug or may be based upon the blood level and/or excretion characteristics of the drug.

The results obtained by suitable clinical methods or by blood level or urinary excretion methods should be correlated with appropriate in vitro dosage performance tests defined by the manufacturer. The in vitro tests should be incorporated into the quality control procedures as part of the Food and Drug Administration's regulations on good manufacturing practices identified in 21 CFR Part 211. The ongoing in vitro quality control procedure would assure product performance on a level in consonance with the in vivo results obtained during the initial stages of development of the particular timed-release product.

The Panel has reviewed § 200.31 (21 CFR 200.31) of the regulations, which regards a timed-release dosage form as a new drug when any such dosage form contains per dosage unit a quantity of active ingredient that is not generally recognized as safe (GRAS) for administration as a single dose under the conditions suggested in the labeling. In such cases, a new drug application (NDA) is required to demonstrate that the drug is properly formulated to release at a safe rate the total dose contained per dosage unit.

The Panel is concerned with the issue of sustained-release formulations of active ingredients placed in Category I. This concern relates to approval of dosage levels of Category I active ingredients in excess of the maximum effective dosage per dosage unit based upon sustained-release or timed-release characteristics of the particular product.

The issue facing the Panel is whether to recommend to the agency that timed-release products be reviewed on a product-by-product basis through the new drug application procedures or whether suitable standards can be developed for testing which can be included in the CCABA drug monograph. The Panel views the exclusive use of the new drug application procedures as eliminating any possible general recognition for timed-release products. The Panel is aware that the drug industry has developed appropriate test procedures for specific timed-release mechanisms which would assure that various timed-release products deliver an effective dosage of active ingredient over a claimed extended period of time between, e.g., 8 and 12 hours. The Panel encourages the drug industry with the assistance of the Food and Drug Administration to develop suitable tests for the standardization of all OTC timed-release CCABA products. The Panel recommends that 4 years be provided for the development of such testing procedures. The Panel is concerned, however, that in the interim some products would be marketed with timed-release claims which, due to poor formulations, would deliver unsafe or ineffective dosages of drugs to the consumer. To assure that safe and effective products are available to the consumer, the Panel recommends that, during this interim period while the drug industry is developing standards with the Food and Drug Administration, sustained-release claims not be permitted in the labeling unless data have been presented before marketing to the Food and Drug Administration documenting that the timed-release preparation exceeds the single therapeutic dosage by an amount sufficient to produce blood levels or other effects that approximate those achieved by multiple administration of single therapeutic dosage units at accepted intervals based on the absorption and/or excretion characteristics of the drug.

The Panel is concerned that after reviewing the safety and effectiveness of active ingredients, a timed-release formulation may modify the safety and ef-

fectiveness in such a way that in essence these products will not be as safe or as effective as the Panel intends.

Any active ingredients or combination of active ingredients that include a claim for time-release will therefore be placed in Category III unless appropriate data can be presented to the Food and Drug Administration as outlined above.

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F. DEFERRAL OF "SORE THROAT" CLAIM

The term "sore throat" is used by consumers to describe a symptom frequently accompanying cough, nasal congestion, or the symptom complex of the "common cold." Sore throat appears as an indication or claim for a variety of products included in submissions reviewed by the Panel.

Ingredients to which sore throat indications and claims are attributed include, in general, local anesthetics and antibacterials. The Panel, working in conjunction with the Food and Drug Administration, has determined that the expertise for evaluating these ingredients for safety and effectiveness resides in the OTC Oral Cavity Panel and has therefore referred these ingredients and the "sore throat" indication and claim to the Oral Cavity Panel.

The Panel notes, however, that while the sore throat may be due to simple irritation resulting from nasal congestion and consequent breathing through the mouth, it may also be due to an infection with potential for serious complications. In the latter circumstances, the patient should not self-medicate and suppress the pain of a sore throat because delay in obtaining medical attention can have serious consequences. Labeling for products intended for relief of sore throat should emphasize that such products are for use only for "minor throat irritation." The products should bear adequate warnings that they are not intended for persistent or chronic sore throat accompanied by fever or other symptoms like headache, rash, nausea or vomiting, or glandular swelling. Labeling should also indicate the potential seriousness of a sore throat and bear adequate instructions for obtaining medical consultation.

G. DRUG MISUSE AND ABUSE

Drug abuse, in its broadest sense, can be described as intentional consumption of a drug for reasons other than legitimate therapeutic uses, often in excess of normally acceptable doses and dosage intervals. Drug misuse generally refers to overuse of a drug for therapeutic purposes due to misinformation or ignorance about its rational use. To the extent that OTC drugs are able to suppress symptoms and through their pharmacological actions also affect other systems to produce overtly perceived effects, i.e., side effects, misuse and/or abuse of OTC products can be expected to occur. The Panel believes, however, that drugs having documented effectiveness, therapeutic utility, and safety when used prudently for self-diagnosable conditions in accordance with label instructions represent a valuable, national public health resource.

Misuse and abuse of drugs is an increasing problem in our society. The Panel is aware of this problem and has addressed it to a limited extent. Of those drugs reviewed by this Panel, the formerly exempt narcotics listed in Schedule V (21 CFR 1308.15), alcohol, sympathomimetics, and belladonna alkaloids appear to be most subject to abuse. It is not within the purview or charge to the Panel to evaluate the numerous psychological, sociological, or economic factors involved in drug abuse. Consequently, the following comments and recommendations are based on medical and scientific data related to safety and effectiveness of these OTC drugs.

The risk of misuse and/or abuse is minimized by restriction on the types of pharmacologic agents in available OTC products, limitations on dosage and concentration of active drug, and adequate and explicit directions for use coupled with appropriate warnings. The Panel also urges that all appropriate measures be directed to reducing the incidence and severity of accidental overdosage, including increased education of the consumer regarding storage of medications, limitations on dosage units per product packages, and employment of safety packaging.

In general, OTC products that have been carefully formulated, thoroughly tested, and adequately labeled are safe when taken in accordance with label instructions for use and dosage. However, when these products are misused or abused, they may have unusual, unexpected, and/or toxic effects. Such drug abuse affects not only the individual himself, but society as a whole. The drug abuse problem is a complex one requiring the joint effort for solution by health care professionals, government, industry, educational institutions, and consumers.

The Panel urges for a balance in educational programs directed to consumers, which illustrate not only the horrors of narcotic addiction, but also the beneficial properties of effective therapeutic agents, their contribution to man's well-being, their undesirable side effects as well as the dangers inherent in all drugs if not properly used. The Panel believes prevention to be the key to the solution of drug misuse and abuse problems, and education to be the key to prevention. Because of the progressive nature of involvement with drugs, it is mandatory that groundwork in drug abuse prevention be laid down for children at an early age and reinforced throughout their lifetime.

There is, at this time, a conspicuous lack of data available on the nature and extent of misuse and abuse of OTC products. The Panel believes it is an obligation of the industry, government, and health care professionals to find out how these products, and especially potentially abusable ones, are being used and misused. The Panel recognizes a need for and recommends attention be directed to definitive, properly conducted studies to provide an indication of the magnitude and severity of the problem attendant to misuse and abuse of OTC products, especially those affecting the central nervous system.

1. *Codeine abuse.* During the time the Panel was in session, the Food and Drug Administration issued a proposed regulation in the FEDERAL REGISTER of September 12, 1972 (37 FR 18741) which proposed to place codeine-containing cough preparations on prescription by modification of 21 CFR 329.20.

At the present time, codeine-containing cough syrups are available for purchase OTC after the patient has signed a registry which records the consumer's name, amount purchased, intended use, and date of purchase. The proposed regulation would have restricted the availability of codeine-containing cough preparations, making such preparations available only by a physician's prescription.

At the request of the Food and Drug Administration, the Panel reviewed the studies on the basis of which the Bureau of Narcotics and Dangerous Drugs (BNDD) (now the Drug Enforcement Administration) asked the Food and Drug Administration to revoke the OTC status and discussed these studies with representatives of the BNDD. In addition, the Panel discussed the potential for codeine abuse with representatives from Food and Drug Administration's Division of Neuropharmacologic Drug Products and discussed with Food and Drug Administration officials aspects of the national policy concerning opium products and production.

This policy was related to the need to reduce illicit drug traffic in narcotics by reducing national imports of opium. A high percentage of imported opium is processed to produce codeine, which is used in codeine-containing OTC cough

preparations. By placing these preparations in a "prescription only" category, their use would be severely reduced and thus the nation's need for imported opium reduced. In addition, BNDD had performed several studies that seemed to indicate a high incidence of abuse of codeine-containing cough preparations, possibly leading to drug addiction and contributing to the illicite drug traffic.

After review of all pertinent scientific data, the Panel concluded that codeine and its salts are safe and effective for OTC use as antitussives when used in accordance with instructions on the label. The potential for abuse of codeine is viewed by the Panel as negligible. When taken by mouth, codeine rarely causes physical dependence. Although codeine can partially suppress morphine withdrawal, it may require high doses in the range of 1,200 to 1,800 mg per day given by injection.

The Panel forwarded to the Commissioner the following statement:

Deliberations of the Panel have resulted in a statement that codeine is safe and effective for OTC use as a cough suppressant. It is further the opinion of the Panel that under usual conditions of therapeutic use, codeine has low dependence liability. On the basis of scientific and medical evidence alone, it is the Panel's opinion that codeine-containing cough suppressant preparations should continue to be available over-the-counter. The Panel recognizes, however, that in the matter now pending before the Food and Drug Administration (removal of prescription exemption for such preparations), considerations go beyond questions of safety and effectiveness alone. The Panel does not deem it part of its function to evaluate factors which are not directly concerned with medical safety and effectiveness. Because there appears to be a conflict between the findings regarding the basic safety and effectiveness of codeine and the removal of the prescription exemption, the Panel strongly urges that FDA clearly identify all factors which lead to FDA's final decision.

As a result, the Commissioner issued a notice withdrawing this proposal in the FEDERAL REGISTER of March 24, 1975 (40 FR 12998), thus retaining codeine-containing cough preparations on OTC status.

2. *Alcohol abuse.* Alcohol, in concentrations up to 42 percent, i.e., 84 proof, is present as a vehicle in a variety of OTC products reviewed by the Panel.

The Panel recognizes a potential for abuse of alcohol contained in OTC cold, cough, allergy, bronchodilator, and antiasthmatic products and recommendations directed to educational programs and need for studies to determine the incidence and severity of misuse and abuse of drugs apply equally to abuse and misuse of alcohol.

H. PEDIATRIC DOSAGE

The Panel is aware that data on the use in children of most drugs in CCABA products are negligible or nonexistent. Yet, pediatric patients comprise a substantial proportion of the population that receives these OTC products.

The dosage that will produce optimum therapeutic effects in a particular patient, adult or child, is dependent upon factors such as the drug itself, individual patient variables such as special sensitivity or tolerance to the specific agent, age, weight and metabolic, pathological, or psychological conditions. Children's dosage calculated by any method that does not take all of these variables into account, therefore, can only be considered general guides.

Definitive pediatric drug dosage should be derived from data obtained in clinical trials with children using protocols similar to those used in adult patients. The Panel recognizes the extreme difficulties attendant upon such trials but also recognizes the immediate need to make recommendations for pediatric dosage pending availability of such definitive data.

Traditionally, pediatric dosage calculations for infants and children have been based on body surface area, weight, or age of the child as a proportion of the "usual adult dose." Dosage calculated on the basis of the age of the child, although convenient, may be the least reliable method because of the large variation in the weight of patients at a specific age. However, for OTC products that have a relatively wide margin of safety, the Panel has concluded that dosage recommendations based on age are the most reasonable since they would be most easily understood by the consumer.

In order to provide the needed dosage recommendations for pediatric patients, the Panel sought the assistance of a panel of experts in pediatric drug therapy. This Special Panel on Pediatric Dosage was convened and met concurrently with this Panel on October 31 and November 1, 1974 and made recommendations. Members of the Pediatric Panel were:

Charles Janeway, M.D.
Sumner Yaffee, M.D.
Jennifer Loggie, M.D., B. Ch.
C. Warren Bierman, M.D.
Louie G. Linarelli, M.D.
Vincent D. Larkin, M.D.
Constantine Falliers, M.D.

Subsequently, the Special Panel on Pediatric Dosage conducted correspondence and review of all pediatric dosage recommendations. These recommendations have been considered in the preparation of this document.

Unless indicated contrarily, the Panel recommends the following guidelines for determining safe and effective pediatric dosages for the individual CCABA ingredients discussed in this document: For infants under 2 years of age, the pediatric dosage should be established by a physician. For children 2 to under 6 years of age, the pediatric dosage is ¼ the adult dosage; for children 6 to under 12 years of age, the dosage is ½ the adult dosage.

The Panel has determined that the labeling terms "baby" and/or "infant" on CCABA products implies that such products have been approved for use in children under 2 years of age. The Panel, therefore, concludes that CCABA products exclude from their labeling the imprecise terms "baby" and/or "infant" unless the ingredient(s) has been specifically demonstrated as safe and effective for children under 2 years of age. In addition, products shown to be safe and effective for children under 2 years of age must provide specific dosages in their labeling for that indication(s). Products with labeling claims for children under 2 years of age not shown to be safe and effective for that age group are considered Category II.

The differences between children under 2 years of age, and other age groups with respect to the anatomy and physiology disorders of their respiratory system, their responses to diseases affecting the respiratory system, and their responses to drugs make general labeling restrictions for this age group essential. For example, infants because of the smaller diameter of their respiratory airways are particularly prone to the complications of respiratory distress during an acute respiratory tract infection such as may occur in the "common cold." Therefore, parents of children under 2 years of age should be advised to consult a physician for diagnosis and individualized therapeutic recommendations, even for symptoms and conditions that are considered appropriate for self-medication in older children and adults. Because of these considerations, the Panel recommends that the general labeling of CCABA products for use in children under 2 years of age requires the advice and supervision of a physician.

The Panel concurs with accepted medical practice that recommends that children be administered a minimum amount or no alcohol. Therefore, alcohol in pediatric formulations should be maintained at the lowest possible concentration. If pharmaceutically possible, products should be formulated without alcohol. Therefore, the Panel recommends that CCABA products containing an alcoholic content greater than 10 percent (weight/weight) should not be given to children under 6 years except under the advice and supervision of a physician.

In the recommendation of the Special Panel on Pediatric Dosage, restrictions on the use of certain drugs were made because of the lack of data and/or experience in the pediatric population. Some drugs may be restricted because of the need for a physician's examination and evaluation of the medical problem for which a drug may be indicated. Still other drugs are not recommended for use in children because of inherent drug toxicity in the pediatric age group. This Panel will indicate, where applicable, pediatric dosages, limits, or warnings, in its discussion below of individual ingredients.

I. INACTIVE INGREDIENTS

A variety of inactive ingredients is used in the manufacture and formulation of products reviewed by the Panel. Such ingredients are intended as flavoring agents, aromatics, vehicles, colorants, sweeteners, etc.

Although the Panel did not review these inactive ingredients, it is the view of the Panel that their safety and the advisability of including them in drug products be reviewed by an appropriate body. Since many of these ingredients are used in the formulation of many drug

products other than those reviewed by this Panel, it is not appropriate that they be dealt with specifically and solely in relation to CCABA products.

For various reasons, individuals may wish to avoid using certain inactive ingredients found in drug products. These reasons may be allergic reactions, idiosyncratic responses, fear of safety (whether valid or not), or personal dislike. It is impossible to make a free choice in this regard unless the full contents of drug products are listed on the label. Therefore, this Panel strongly recommends that the Food and Drug Administration require full ingredient labeling of inactive as well as active ingredients in descending order of quantities present in all drug products. In support of this position the Panel notes that food products are already required to have such labeling, and since the purpose of a drug is to alleviate symptoms of disease, it would seem much more compelling to have this information on all drugs.

In line with the Panel's desire to expose the consumer to the smallest number of ingredients possible, the Panel has previously recommended that marketed products contain only those ingredients essential to the product. (See part II. paragraph C.2. above—Limitation of Ingredients in Combination Products.)

Although chloroform was reviewed, and considered by the Panel to be an inactive ingredient, it was reviewed again at the special request of the Food and Drug Administration, because of reports suggesting that it is carcinogenic (Refs. 1 and 2). A discussion can be found later in this document. (See part IV. paragraph B.2.b. below—Chloroform.)

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J. ADVANTAGES OF SINGLE INGREDIENT PRODUCTS

OTC drug combination products seem to provide the public with many options from which to select the preparation most likely to relieve a symptom or group of symptoms. The combinations available would seem on the surface to be rational. The Panel has discussed CCABA combination products earlier in this document. (See part II. paragraph C.1. above—General combination policy.) However, the individual may need or tolerate only one of the ingredients in the combination product and the presence of the others may be unnecessary or, because of side effects or idiosyncratic reactions, their presence may preclude use of the combination.

Great variability with regard to side effects induced by drugs is seen among patients. Common examples are drowsiness caused by antihistamines and nervousness and sleeplessness caused by ephedrine. Furthermore, the ratio in which the components exist in the combination will be unsuitable for some persons. Although these effects and the drugs producing them are familiar to physicians and pharmacists, the public is unlikely to identify the ingredient causing the side-effect if the ingredient is present in a combination. This difficulty is largely avoided with single ingredients, which many physicians prefer to prescribe. With a single ingredient, whether available OTC or on prescription only, the patient can recognize the drug's action with relative ease and can adjust the dosage according to need. Experience gained in this way could be very useful to the patient on occasions of future need for self medication.

Single ingredients are rarely available among CCABA OTC drugs. Since many physicians prefer to treat with single ingredients, it seems logical for the public to have the option to medicate themselves with single ingredients also.

In summary, availability of individual ingredients would provide increased opportunity for the public to evaluate OTC drugs and allow the public to avoid taking two or more drugs where one might suffice. This will promote more specific and possibly safer self-medication.

It is strongly recommended therefore, that any active ingredient marketed in OTC preparations for cold, cough, etc. be equally available OTC as a single ingredient and in a form equally convenient to administer.

K. ADVERTISING

The Panel is aware that the role of the Food and Drug Administration is to regulate labeling of over-the-counter drugs and the role of the Federal Trade Commission is to enforce adherence to such labeling in advertising. In addition to recommending specific labeling claims, warnings, and dosages, the Panel would like to make some general comments and recommendations regarding advertising of drugs.

Advertisements extend the label beyond the pharmaceutical counter or medicine cabinet. The public may well receive most of its attitude toward CCABA remedies from advertisements—particularly television advertisements.

For this reason the Panel strongly urges the Federal Trade Commission to challenge any advertisement which:

1. In any way negates or dilutes the information on the label, especially the contraindications and/or warnings;

2. Suggests or leans heavily on words, phrases, and portrayals that lead the lay person to assume that the product is to be used in any manner not recommended in the monograph established below, or that it cures when in reality it only alleviates symptoms.

The Panel further recommends that advertisements for CCABA remedies not be placed where they can promote or suggest use by children, and if such an advertisement is placed where numbers of children may learn of the indications for the product, that such advertisement contain clear and specific warnings and contraindications concerning child use.

L. STATEMENT ON CCABA COMBINATION PRODUCTS CONTAINING ASPIRIN

The Panel is aware that certain individuals develop manifestations simulating an allergic reaction within 15 to 45 minutes after taking 300 to 600 mg of aspirin (acetylsalicylic acid) (Ref. 1). Such reactions may occur even though aspirin has previously been well tolerated by these individuals for many years. The major manifestation of such an allergic type reaction to aspirin is asthma, which may be of such severity as to be life-threatening. These manifestations are those seen in acute allergic reactions. Other manifestations include intense nasal stuffiness and urticaria. However, all efforts to demonstrate an allergic mechanism to account for these reactions have failed.

In a study of nine analgesic drugs with respect to their capacity to induce bronchial reactions in aspirin-sensitive asthmatic patients and their ability to inhibit prostaglandin synthetase activity, those five drugs (aspirin, indomethacin mefenamic acid, flufenamic acid, and phenylbutazone) active in causing asthma were also active in inhibiting the enzymes (Ref. 2). Of the nine analgesics, four drugs (salicylamide, paracetamol, benzydamine, and chloroquine) lacking the capacity to induce asthma on challenge in aspirin-sensitive asthmatic patients also lacked the capacity to inhibit prostaglandin synthetase activity. Since some prostaglandins have bronchoconstrictor activity whereas others have bronchodilator activity, it was postulated that aspirin and other drugs giving asthma on challenge may do so by modifying prostaglandin synthesis. Inhibitors of prostaglandin biosynthesis such as aspirin should not be given to patients with aspirin-sensitive asthma (Ref. 2).

The available clinical evidence indicates that the presence of the acetyl group in aspirin is essential for such reactions to occur since sodium salicylate and other salicylates are well tolerated in aspirin-sensitive persons.

The frequency of adverse reactions to aspirin among asthmatic children 6 to 16 years of age is reported to be 1.9 percent (Ref. 3), and among adult asthmatics the reported frequency exceeds 3 percent and may be substantially higher (Refs. 1, 4, 5, and 6). There are at least two reports of death following the ingestion of aspirin (Refs. 7 and 8). Asthma may appear for the first time, after taking aspirin, in individuals who may have previously tolerated aspirin. Therefore, the Panel feels that a warning limited to the statement that aspirin-containing preparations be avoided by those with already existing asthma would be inadequate.

A common history in individuals who previously tolerated aspirin is long-standing perennial rhinitis, chiefly characterized by nasal stuffiness. Nasal polyps are very common but are not invariably present. Asthma may or may not have been present. The Panel is concerned that individuals having tolerated aspirin in the past may develop a severe reaction, usually an asthmatic attack, following the taking of a CCABA product containing aspirin. If aspirin is present in a combination drug product, aspirin is usually not recognized as the cause of

the reaction until such episodes occur once or twice more.

The association between nasal polyps, asthma, and aspirin sensitivity has been recognized for many years, and there are many reports in the literature (Refs. 1, 3, and 9). Eosinophilia is the rule in these patients and this should be considered as part of the syndrome. The yellow dye, tartrazine, and the anti-inflammatory drug, indomethacin, are also reported to cause asthma in these patients (Ref. 9).

The Panel recognizes that prevention is the logical course, which includes recognition of the syndrome and proper instruction given to the patient. However, the Panel notes that the presence of aspirin in combination with other drugs can lead to ingestion of aspirin by error, a point frequently made by patients. Furthermore, the first reaction of this kind in aspirin-sensitive individuals will often go unrecognized if aspirin is in combination with other drugs. For this reason the Panel concludes that the availability of aspirin in combination drug products can be expected to lead to more of these severe reactions than would occur if aspirin were only available as a single ingredient.

The OTC drugs under review by the Panel are frequently taken by consumers in whom reactions to aspirin are most frequent. The Panel notes that other analgesics like acetaminophen are available and may be included in specific combination products. (See part II. paragraph C. above—Principles Applicable to Combination Products.) For this reason, the Panel concludes that CCABA combination products containing aspirin (acetylsalicylic acid) should be labeled under the heading *"Warning"*: "This product contains aspirin and should not be taken by individuals who are sensitive to aspirin."

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M. GENERAL STATEMENTS ON THE DETERMINATION OF SAFETY AND EFFECTIVENESS FOR CCABA PRODUCTS

1. *Determination of safety.* a. *Single drugs.* In deciding on the safety of a drug or combination of drugs, both animal and human studies were considered.

Although animal studies were of interest, they were seldom very helpful because it would be unusual for a drug to reach the market without satisfactory animal safety data. The animal data usually related to levels of the drug that might cause death and the effect of the drug on various organs such as the bone marrow, liver, and kidneys.

Major attention was paid to information related to adverse effects in humans, both adults and children. A knowledge of the pharmacology of the drug or drugs under consideration made it possible to look specifically for adverse effects in one or more systems. It was important that there be studies in which the drug was compared with a placebo. In addition, blood levels related to toxic effects were very useful and could be related to various dosages and routes of administration. Examples of the great variety of possible toxic effects are as follows:

(1) An adverse effect might be present but this might not be very serious and could be dealt with by careful labeling, e.g., the drowsiness caused by many antihistamine drugs.

(2) A drug might have abuse potential. For example, the abuse potential for codeine was considered small, but the abuse potential for stramonium was considered very high.

(3) The effect of repeated doses of the drug had to be considered, e.g., the rebound nasal congestion which can occur with repeated doses of nasal decongestant drops or sprays.

(4) A possible excessive therapeutic effect was considered, e.g., the drying effect of drugs from different pharmacologic groups (antihistamines and anticholinergics) on the bronchial tree.

(5) The possible depressant effect other than that related to the symptom under consideration, e.g., a cerebral depressant effect of an antitussive.

(6) The route of administration of drugs had to be considered, for example, the local effect on the bronchial tree of drugs used in the treatment of asthma where these were administered in an aerosol. Another example is the use of suppositories of theophylline that could be additive to theophylline given by mouth.

(7) The seriousness and frequency of known idiosyncratic reactions might be critical, e.g., the very serious adverse effects of aspirin in some patients with asthma.

(8) There might be interactions with other drugs such as the serious result of taking ephedrine with a monoamine oxidase inhibitor which would cause a severe rise in blood pressure.

All the above were considered, and in addition, information was sought regarding any differences that might occur when the drugs were given to children of various ages as compared with adults. Children less than 1 year tend to metabolize drugs differently from older children and, as this was difficult to predict, this was one factor leading to the decision of the Panel not to label drugs for OTC use in children under 2 years except under the advice and supervision of a physician. (See part II. paragraph H. above—Pediatric Dosage.)

The importance of clear labeling of warnings and cautions was continually considered, and it is recommended that the public be educated to read labels carefully and to take the warnings and cautions seriously.

b. *Drug interactions.* There is little, if any, documentation of drug interactions between OTC drug products or between OTC drug products and prescription products and only speculation can be offered regarding such potential interactions. Even well-documented drug interactions may depend on drug dosage levels not usually attained with OTC products. Therefore, in considering the safety of OTC drugs, one must consider not only possible effects of single drugs but also possible adverse effects of interactions between drug combinations. The Panel has recommended appropriate labeling warnings where there are serious concerns.

2. *Determination of effectiveness.* In determining effectiveness, it was necessary to consider each pharmacologic group separately although certain general principles applies to all groups.

Animal studies were seldom very helpful except in the case of antihistamines where one of the requirements for efficacy was the capacity of the drug to decrease or suppress anaphylaxis and the effects produced by histamine in animals.

Major attention was paid to clinical studies especially where the double-blind technique could be employed. In some situations the ability to do a crossover study was of additional value. Studies in which there were objective measurements with proper controls and statistical analysis were of considerable weight in the Panel's decision to place an ingredient in Category I. However, certain drug actions made such objective measurements extremely difficult or impossible and therefore, large well-controlled subjective studies were considered of reasonable use. Partially controlled and uncontrolled clinical studies were of very limited value but both were considered by the Panel. Clinical experience of a general nature, if documented by qualified experts, added somewhat to the final decision. It was considered particularly useful if similar results were obtained.

In some instances, the Panel considered the Drug Efficacy Study data. The Drug Efficacy Study of the National Academy of Sciences—National Research Council (NAS/NRC) reviewed the data submitted to the Food and Drug Administration to support effectiveness of only marketed products that had re-

ceived premarket clearance through a New Drug Application (NDA) for safety prior to 1962. The Panel in reaching its decision considered all the studies available including information from the Drug Efficacy Study.

Examples of the different types of studies (all of which should be placebo controlled) used by the Panel to assess different drug groups are as follows:

a. Antitussives are best assessed by objective cough-counting techniques. The antitussive can be tested by decreasing induced cough or by decreasing the cough in patients with chronic cough.

b. Expectorants may be assessed by large double-blind crossover subjective studies in patients with chronic lung disease or randomized double-blind studies in patients with acute upper respiratory infections. These studies are acceptable because objective techniques for assessing the expectorant action of a drug are not yet satisfactory and require further development.

c. Bronchodilators are best assessed by objective measurements of pulmonary function in asthmatics where a significant improvement in pulmonary function can be shown after the use of the drug.

d. Antihistamines require the study of large groups of patients with strict double-blind control using a subjective evaluation of the effect of the drug on allergic rhinitis or on the symptoms of the "common cold". These clinical subjective studies are acceptable as there is no definite objective technique for measuring the effect of antihistamines in these conditions. Anticholinergic drugs which are used in the treatment of rhinitis with rhinorrhea require clinical testing similar to that of the antihistamines.

e. Nasal decongestants which relieve obstruction to the nasal passages are best assessed by objective measurements of resistance to air flow through the nose. In this way comparisons of the drug and the placebo can be made using data of airway resistance measurements.

Although all the evidence related to the effectiveness of a drug was considered, the above studies in the various pharmacologic groups had the greatest influence in determining a Category I classification.

It was extremely difficult to judge the effectiveness of combinations of ingredients because of the many different dosages involved and the difficulty in determining the effect of each individual ingredient in the combination. The Panel considered it reasonable that Category I ingredients from different pharmacologic groups differed sufficiently from one another to reduce the likelihood of a competitive or potentiating effect between ingredients, and their combination was therefore considered effective. There are some exceptions to this and these exceptions are discussed in the section on combination drugs. (See part II. paragraph C.—Principles Applicable to Combination Products.)

To assist in the testing of ingredients in the future, the Panel developed clinical testing procedures for each pharmacologic group. These procedures have been included in the "Data Required for Evaluation" sections following the ingredient(s) statements for each pharmacologic group.

N. AEROSOL DOSAGE FORMS OF DRUGS UTILIZED IN CCABA PRODUCTS

The utilization of the pressurized, self-contained and self-propelled "aerosol" dosage forms in delivering pharmaceuticals was begun in the 1950's when advances in the technologies of propellants, valves, and containers made possible the accurate delivery of metered doses for direct inhalation into the respiratory system. Development in the areas of fine particle technology and different aerosol systems kept pace with the evolution of specialized valves and actuators, containers of diverse materials such as glass, coated metals and plastics, and a variety of propellant gases such as the halocarbons, compressed gases (nitrogen, carbon dioxide, nitrous oxide), and hydrocarbon gases (butane, isobutane, pentane).

The Panel is aware of the advantages and disadvantages of the pressurized drug products that were the subject of submissions to the Panel.

Among the advantages may be listed:

1. Aerosol products are permanently sealed units, and thus their contents are maintained in a stable form that is protected from accidental contamination by organisms, atmospheric gases, moisture, and sunlight that are sometimes encountered with the use of ordinary containers that are repeatedly opened.

2. The utilization of specialized valves and adapters permit the release of mists, sprays, or true aerosols (particles suspended in gas), in a controlled manner that assures the rapid administration of the aerosolized drug. This is particularly useful when prompt onset of action is desirable.

3. Metering valves and containers are available in compact form, so as to permit the consumer to carry the product on his person with little inconvenience and with quick accessibility when medication is required.

4. Aerosol products designed to emit an intermittent or continuous spray of medicaments into the atmosphere of a room are capable of producing aerosolized mists containing particles that are fine enough to be inhaled and thus exert their effect rapidly in the respiratory tract.

In recent years the advantages of the aerosolized forms of drugs for treatment of bronchial asthma and the transitory symptoms of the "common cold" have been challenged because of potential toxicities. These include the cardiotoxicity potential of the halocarbon propellent, fluorocarbon 11. Several studies have been reported that indicate that the propellant can be absorbed into the blood with a persistence of a small quantity in the blood after 1 hour.

Reports of accidental sudden deaths following the inhalation of aerosols emptied into a plastic bag indicate an abuse potential that cannot be overlooked.

More recently predictions based on the use of computer models have warned about the possibility that halocarbons released into the air from aerosol products may be the cause of depletion of the ozone layer in the stratosphere. Concern has been expressed that if these predictions are accurate then the protective elements of the stratosphere against ultraviolet radiation may become impaired.

The Panel, therefore, concludes that although aerosol products do possess inherent advantages for specialized application of drugs in bronchial asthma and other respiratory conditions, the possibility of toxic effects of the halocarbon propellants should be carefully evaluated by a suitable Panel of experts in this area.

O. CCABA PRODUCT LABELING CLAIMS NOT SUPPORTED BY SCIENTIFIC EVIDENCE

The Panel has reviewed the submitted labeling claims made for CCABA products. It is interesting to note that products sold for relief of symptoms of the "common cold" and allergies are probably the largest category of OTC drug products on the United States OTC drug market. In fact, there are estimates by the Food and Drug Administration that as many as 50,000 different OTC CCABA drug products are currently marketed. Because of this vast array of products, the consumer is often faced with a myriad of confusing claims, which are not only vague and hard to comprehend, but also make it almost impossible for the consumer to distinguish between these products.

One of the primary functions of this Panel is to minimize this confusion by clarifying the labeling. In that way the ordinary individual who purchases an OTC drug product for the relief of symptoms, e.g., of the "common cold" or allergies, will understand exactly what the product will do for him, the limits of the product's capability, and the cautions to be observed when using that product. It is also a basic function of the Panel to attempt to reduce confusing labeling claims to a reasonably concise number of understandable claims, permitting the consumer to easily distinguish between various CCABA products. The Panel believes that at the present time this is not possible since the labeling that appears on many currently marketed CCABA products tends to be overly complicated, vague, unsupported by scientific data, and in some cases is false and misleading.

The Panel understands the drug industry's desire to market OTC drug products for the relief of symptoms of the "common cold" or allergies by suggesting uniqueness or superiority of one product over another. But uniqueness or superiority must be proven scientifically or labeling will mislead and unduly confuse the consumer. For example, if one ingredient can be demonstrated to be superior to another because of greater effectiveness, then the consumer should be so informed. Conversely, if two ingredients are indistinguishable with regard to effectiveness, e.g., both are equally

effective in suppression of cough, then it is misleading to claim superiority for one of the ingredients. In this regard, the Panel wishes to make clear that its function is not to compare various ingredients in order to determine the OTC drug of choice. Rather, the Panel determines only safety and effectiveness for active OTC CCABA ingredients, as well as proper dosage ranges for OTC drug use. In reviewing the scientific literature for CCABA ingredients, it is clear that ingredients of the same pharmacologic group that are Category I, i.e., generally recognized as safe and effective, have similar effectiveness in the dosage ranges recommended. Consequently, the Panel concludes that all claims which imply superiority of one product over another, both of which contain Category I ingredients in the same pharmacological group, should be prohibited from the labeling of CCABA products. These claims would include such phrases as "Superior to ordinary" and "Specially improved or selected ingredients".

In addition, the Panel has determined that statements alluding to superiority due to greater potency, such as "extra strength" or "contains more active ingredient per dose", are also misleading unless fully documented. The Panel can find no justification for claiming more activity per dose for one Category I ingredient over another because there is no scientific merit from a therapeutic point of view between a product containing 15 mg of a drug A and another containing 30 mg of drug B if they are similarly effective. Unsubstantiated claims for "extra strength" or "contains more active ingredient per dose" or "higher dose level" or "stronger than" are therefore misleading. However, assuming that claims of greater potency were based on documented facts, such increase in potency might also indicate an increase in the potential side effects. Under such circumstances the Panel feels that such claims are misleading to the consumer.

Misleading superiority claims may also manifest themselves as claims that state or imply actions peculiar to a particular product, when in fact those claims are applicable to all OTC drug products or all Category I ingredients of the same pharmacologic group. Thus, for example, if two different OTC cough products contain different Category I antitussive ingredients, it would be misleading to make such claims as "specially formulated" or "specially selected ingredients". This view would, of course, also be applicable to combinations of appropriate CCABA ingredients or combinations of CCABA and non-CCABA ingredients. Thus, claims such as "teamed components" would also be considered misleading by the Panel.

Another area of concern to the Panel is claims implying a unique physiological action that either has no scientific foundation or meaning or that will be meaningless to the consumer. Such claims include pseudo-medical terms such as "antiallergic", or pseudo-medical activities such as "gets at the roots of", "fights", "wakes up", and "multiaction". Some claims mislead the consumer into believing a product has a unique action, when in fact that pharmacologic action is shared by all similar OTC drug products containing active ingredients from the same pharmacologic class. Examples include claims that an ingredient "travels through the bloodstream" or "works internally". All drugs taken internally "work internally" and virtually all drugs taken internally are absorbed into the bloodstream. Thus, these claims are also not appropriate in OTC labeling.

Finally, the Panel is concerned about vague generalizations relating to time that do not actually relate to the directions or indications. This is especially true where the time stated in the claim is indeterminate. Thus, claims such as "fast" and "prompt" should not appear on labels unless they are directly correlated to the directions for use permitted in the monograph.

P. CCABA PRODUCT NAMES AND LABELING CLAIMS ASSOCIATED WITH DISEASES AND RELATED SYMPTOMS

The Panel has made a clear distinction in this document between the treatment for the relief of the symptoms of a disease, e.g., cough, runny nose, and the treatment of the disease itself, e.g., "common cold." With few exceptions, CCABA products are indicated only for the treatment for the relief of symptoms. The most common disease associated with CCABA products is the "common cold." The Panel has discussed this respiratory disease earlier in this document. (See part II. paragraph B.3. above—The "common cold.") The Panel concludes that there is no demonstrated safe and effective OTC active ingredient or combination of active ingredients acceptable for specific treatment of the "common cold." Consequently, the Panel recommends that product names or labeling claims that infer or suggest a direct relationship to the "common cold," e.g., "cold medicine," "cold formula," "for relief of colds," should not be allowed. Such statements may mislead the consumer into believing that these products prevent, treat, or cure the disease itself.

The active ingredients reviewed by the Panel and included in currently marketed CCABA products are generally used for the treatment or relief of the symptoms of disease. The Panel concludes that if labeling is restricted to the proven pharmacologic activities of the active ingredients in CCABA products, reference in labeling to the specific activities of such ingredients in alleviating symptoms is acceptable. The Panel has summarized the commonly encountered symptoms and the acceptable pharmacologic groups earlier in this document. (See part II. paragraph B. above—Diseases and Related Symptoms Relieved by OTC Cold, Cough, Bronchodilator and Antiasthmatic Products.)

For drugs used to treat the symptoms of the "common cold," the Panel recommends that in addition to the acceptable claims (Category I) for specific pharmacologic groups, the following phrases may be used: "(symptoms) as may be associated with the 'common cold' " or "as may occur in the 'common cold' ". An example for a product containing an antitussive would be "For cough as may occur in the 'common cold'."

On the other hand, the Panel finds that certain OTC bronchodilator active ingredients are safe and effective for the treatment of asthma. This disease is effectively treated by OTC products but requires prior diagnosis of asthma by a physician. Bronchodilators serve to relieve the primary manifestations of asthma, shortness of breath, which is caused by widespread narrowing of the airways due to airway wall muscle spasm. The Panel recognizes that bronchodilators cannot prevent or cure the disease but are effective in relieving the primary symptoms. Because of these unique symptoms and because the Panel believes these products should be easily identifiable and accessible to those afflicted with the disease, the Panel concludes that use of the term "asthma" in labeling of products containing Category I bronchodilator active ingredients, either as part of a product name, e.g., "asthma medicine", or appearing alone in labeling claims, e.g., "treatment of asthma", is acceptable. The Panel is of the opinion that reference to asthma in labeling is not misleading and further, is essential for those individuals diagnosed by a physician as having the disease. This of course is acceptable, based upon the Panel's recommendation later in this document that the following warning be on all products containing bronchodilators: "Do not use this product unless a diagnosis of asthma has been made by a physician". (See part V. paragraph B.1. below—Category I Labeling.)

The Panel also recognizes that allergic rhinitis (such as hay fever) is a very common disease. Unlike the "common cold," most affected individuals understand the etiology of such a disease and realize that it cannot be prevented or cured by OTC antihistamines or nasal decongestants. However, as was the case with asthma, the manifestations of this disease can be treated with such a product. Here again, it is the Panel's conclusion that it is also acceptable for the terms "hay fever", and "allergic rhinitis", to appear in labeling of products containing Category I ingredients either as part of a product name, e.g., hay fever medicine, or appearing alone in labeling claims, e.g., "Dries running nose as may occur with allergic rhinitis", or "For treatment of hay fever".

Q. INGREDIENT EQUIVALENCE

The Panel recognizes that the ingredients submitted and reviewed may exist in chemical forms other than those considered in this document. The Panel notes that other salts, esters, and complexes of these ingredients may be available, which may be therapeutically equivalent to the forms of the ingredients considered by the Panel. In recognition of this fact, the Panel concludes that provided that there are suitable data to establish bioequivalence and safety, salts, esters, and complexes of ingredients dis-

cussed in the monograph would be acceptable. However, it is essential that the dosage used be equivalent to the dosage of the ingredient in the monograph.

INTRODUCTION TO PHARMACOLOGIC CLASSIFICATIONS

Not all CCABA products are used for the same purpose, nor should the requirements for effectiveness be the same. In an attempt to classify CCABA active ingredients and their products it was necessary to distinguish between the pharmacologic activities and resulting effectiveness for labeled claims of these products.

The following classifications of CCABA product ingredients was developed by the Panel in an attempt to simplify categorization of ingredients and thereby eliminate labeling confusion:

Antitussives
Expectorants
Bronchodilators
Anticholinergics
Antihistamines
Nasal decongestants
Miscellaneous active ingredients

III. ANTITUSSIVES

A. GENERAL DISCUSSION

An antitussive agent specifically inhibits or suppresses the act of coughing. Direct inhibtion may result from: depression of medullary or higher centers in the brain; diminishing the sensitivity of the cough receptors in the membranes lining the throat and respiratory passageway; interruption of the transmission of the cough impulses to the brain or to the muscles that are involved in the act of coughing; and by removal of irritants and excessive secretions through the improvement in bronchial drainage.

In theory, cough suppression may be produced indirectly by one of two mechanisms: A soothing action on the irritated or inflamed throat, which would in effect decrease the sensitivity of special nerve endings or cough receptors in such membranes; and a relief of spasm or localized constriction of the airway. This is known to occur in asthma or following the inhalation of an irritant.

The Panel has followed the presently accepted medical approach and has classified antitussives according to their principal site of action.

1. Centrally acting antitussive agents produce cough suppression by acting on the central nervous system to depress the medullary (brain) cough center and thus raise its threshold for afferent (incoming) cough impulses. These agents may be further subdivided into narcotic antitussives, such as codeine, and nonnarcotic antitussives such as dextromethorphan.

2. Peripherally acting antitussive agents act on the nerve receptors within the respiratory tract. Cough suppression may be produced by several different mechanisms such as a local anesthetic (pain deadening) or analgesic (pain suppressing) action on the mucosa of the respiratory tract; enhancing bronchial airway drainage by reducing the viscosity (thickness) of retained secretions, which may occur with effective expectorant agents or with adequate humidification of the airway; relaxation of the smooth muscle of the bronchial airway in the presence of spasm; or a soothing (demulcent) effect on the irritated throat and bronchial airway walls.

The narcotic antitussives have traditionally been the most effective agents available for suppressing cough. Because of its low abuse potential, codeine, the best known and most widely used antitussive in this group, has been considered safe for OTC use. Except in unusual circumstances in which cough is associated with pain, e.g., in pleurisy, the more potent narcotics such as morphine are not used because of their potential for acute toxicity from overdosage (respiratory depression) and abuse potential. Such drugs are best administered under medical supervision.

Nonnarcotic antitussives, such as dextromethorphan, act by selective suppression of the central cough mechanism and have no significant abuse liability. Therefore, they would seem to be more advantageous for use in treating cough and also for use in individuals who seem psychologically predisposed to drug dependence.

In general, the antitussives available for OTC use are and should be designed to diminish coughs associated with acute, self-limiting conditions that cause irritation to the respiratory airway. Since it is highly unlikely that such conditions would persist for more than 1 week, the Panel has limited the period of administration of these antitussives to a maximum of 7 days. A persistent cough for more than 1 week or one accompanied by high fever, rash, or persistent headache may be indicative of a serious disease, which should be treated by a physician and does not lend itself to self medication by antitussives. (See part II. paragraph B.4. above—Cough.) In asthma, bronchitis, pulmonary emphysema, and a number of other respiratory diseases, there is often an over production of secretions which accumulates in the airway and results in a cough productive of thick sputum. The suppression of cough by antitussives in such instances would impair clearing of the airway and could be harmful.

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Labeling

Consumers often have difficulty understanding the intended meaning of OTC drug labeling. The Panel concludes that use of vague words, or words which imply a greater effectiveness than other similar OTC products, is false and misleading. The Panel has reviewed the labeling that was submitted for antitussives and for other pharmacologic groups and has attempted to explain why some labeling is acceptable, objectionable, or questionable.

In the case of antitussives, the Panel has reviewed the symptoms of cough and the mechanisms by which the physiologic response is produced. Cough occurs in healthy individuals as a mechanism for clearing the airway of any obstructing mucus or inhaled foreign material. As indicated above, medications that suppress the act of coughing by reducing the number of coughs and/or the intensity of coughing are known as antitussive drugs. Based upon the previous discussion of cough and the discussion of antitussives, the Panel concludes that the following indications are acceptable labeling claims for generally recognized safe and effective antitussives (cough suppressants) for the temporary relief of cough: "Cough suppressant which temporarily reduces the impulse to cough". "For the temporary relief of coughs due to minor throat and bronchial irritation as may occur with the common cold or inhaled irritants". "Temporarily quiets coughing by its antitussive action". "Temporarily helps you cough less". "Temporarily helps to quiet the cough reflex that causes coughing".

Because of the lack of clinical studies in children under 2 years of age, the Panel was unable to determine an OTC dose for this age group. Based upon the lack of available data, the Panel recommends the following warning for products containing antitussives: "Do not give this product to children under 2 years except under the advice and supervision of a physician".

Since a persistent or chronic cough may be a sign of a serious condition requiring medical intervention and should be brought to the attention of a physician, the Panel recommends that all labeling for antitussive products bear the following warning: *"Caution:* A persistent cough may be a sign of a serious condition. If cough persists for more than 1 week, tends to recur, or is accompanied by high fever, rash or persistent headache, consult a physician".

In asthma, bronchitis, pulmonary emphysema, and a number of other respiratory diseases, there is often an overproduction of secretions, which accumulate in the airways and results in a cough that produces thick mucus. The suppression of cough by antitussives in such instances would impair clearing of the airway and could be harmful; therefore, the Panel recommends the following additional *"Warning"*: "Do not take this product for persistent cough such as occurs with smoking, asthma, emphysema, or where cough is accompanied by excessive secretions except under the advice and supervision of a physician".

B. CATEGORIZATION OF DATA

1. *Category I conditions under which antitussive ingredients are generally recognized as safe and effective and are not misbranded.*

Category I—active ingredients

The Panel has classified the following antitussive active ingredients as general-

ly recognized as safe and effective and not misbranded:

Codeine preparations: Codeine, Codeine alkaloid, Codeine phosphate, Codeine sulfate
Dextromethorphan
Dextromethorphan hydrobromide
Diphenhydramine hydrochloride

a. *Codeine preparations (codeine, codeine alkaloid, codeine phosphate, codeine sulfate).* The Panel concludes that codeine and its salts are safe and effective for OTC use as antitussives as specified in the dosage section discussed below.

(1) *Safety.* Side effects such as drowsiness, light headedness, excitement, loss of appetite, nausea, vomiting, headache, abdominal discomfort and constipation with oral doses of 20 mg of codeine have not been significantly greater than with placebo (Ref. 1). The Panel has reviewed the literature and finds that respiratory depression may occur but is usually seen when codeine products are used as prescription medication with dose levels of 120 mg every 4 hours which results in the codeine having analgesic activity similar to that of 10 mg of morphine (Ref. 2). Such high doses of codeine would present a real hazard in certain cases of respiratory disease associated with a tendency towards carbon dioxide retention. By central depression of respiration, the exchange of oxygen and carbon dioxide would be impaired and there would be a tendency for the carbon dioxide to accumulate in the blood resulting in or aggravating respiratory acidosis with a dulling of the senses progressing to coma. As little as 60 mg of codeine in adults has produced measurable respiratory depression, judging from carbon dioxide response curves (Refs. 3 and 4). This has not been apparent with the doses approved for OTC use. In an infant, doses of 10 mg every 2 hours for 10 doses has led to deep coma (Ref. 5). Death has occurred from overdosage with codeine in the range of 875 to 1,750 mg but effects were complicated by the presence of other central nervous system depressants (Ref. 6).

The Panel believes the potential for abuse of codeine is negligible (Refs. 7, 8, and 9). It is further the opinion of the Panel that under usual conditions of therapeutic use, codeine has low dependency liability. Codeine may cause addiction, but requires consistently high daily dosage (Ref. 9). (See part II. paragraph G. above—Drug Misuse and Abuse.)

(2) *Effectiveness.* A paper by Eddy et al. (Ref. 10) summarized all the data in animals and indicates the varied techniques used and results obtained. Practically all animal studies have demonstrated the ability of codeine to suppress the cough reflex.

Studies of experimentally produced cough in man were also reviewed by Eddy et al. (Ref. 10). Cough-inducing agents used were citric acid aerosol, ammonia vapour, acetylcholine aerosol, peppermint water spray, and paraldehyde. The dose of codeine ranged from 5 mg to 120 mg with most investigators using 15 to 30 mg and they were able to demonstrate a cough suppressant effect in humans.

Eddy's review of 33 clinical trials by 16 investigators (Ref. 10) indicated that codeine in doses ranging between 10 to 60 mg was an effective cough suppressant in a wide variety of disease states associated with cough. Twenty-four of these studies employed objective cough-counting techniques. All had placebo controls, and many compared codeine with other drugs as well. While all of the objective studies employed patients with chronic cough (Refs. 11 through 16), two of the subjective studies employed patients with an acute cough due to an upper respiratory infection (Refs. 17 and 18).

The technique of employing citric acid aerosols to stimulate the cough reflex in healthy subjects (Ref. 19) has also been used to demonstrate the effectiveness of codeine as an antitussive in dose ranges of 15 to 30 mg.

There are no well-controlled studies on the antitussive activity of codeine in children, and hence, dosage recommendations in children have been based on the general experience of a Pediatric Panel, which reviewed these recommended dosages. (See part II. paragraph H. above—Pediatric Dosage.) Because the majority of clinical trials have been in chronic cough, the Panel has accepted the principle that the effectiveness of codeine in coughs due to upper respiratory infection may, in large measure, be extrapolated from the information on antitussive activity in chronic cough. This is further supported by an extensive clinical experience with the use of codeine over the past 50 years.

Because of abuse liability of codeine if available as a single ingredient in unlimited supply, the Panel concurs with the present Drug Enforcement Agency regulations, which limit the sale of codeine over-the-counter. These regulations limit the amount of codeine or its salts contained in an OTC product to 200 mg per 100 ml for liquid preparations or 200 mg per 100 gm for solid dosage forms (21 CFR 1308.15(b)(1)). These regulations further specify that codeine for OTC purchase must include one or more nonnarcotic active medicinal ingredients in sufficient proportion to confer medicinal qualities upon the product other than those possessed by codeine alone (21 CFR 1308.15(b)). In addition, these regulations limit OTC sale of such codeine containing products to quantities not exceeding 120 ml or 24 dosage units (21 CFR 1306.32(b)).

(3) *Dosage.* Adult oral dosage is 10 to 20 mg every 4 to 6 hours not to exceed 120 mg in 24 hours. Children 6 to under 12 years oral dosage is 5 to 10 mg every 4 to 6 hours not to exceed 60 mg in 24 hours. Children 2 to under 6 years oral dosage is 2.5 to 5 mg every 4 to 6 hours not to exceed 30 mg in 24 hours. For children under 2 years, there is no recommended dosage except under the advice and supervision of a physician.

(4) *Labeling.* The Panel recommends the Category I labeling for antitussive ingredients. (See part III. paragraph B.1. below—Category I Labeling.) In addition, the Panel recommends the following specific labeling claims referrable to a central mechanism of action: (i) *Indications.* "Calms the cough control center and relieves coughing".

(ii) *Warnings.* (*a*) "May cause or aggravate constipation".

(*b*) "Do not give this product to children taking other drugs except under the advice and supervision of a physician".

(*c*) "Do not take this product if you have a chronic pulmonary disease or shortness of breath except under the advice and supervision of a physician".

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b. *Dextromethorphan, dextromethorphan hydrobromide.* The Panel concludes that dextromethorphan and dextromethorphan hydrobromide are safe and effective for OTC use as antitussives as specified in the dosage section discussed below.

(1) *Safety.* Dextromethorphan is the dextrorotatory isomer of the morphinan molecule which, unlike the levo isomer, has no analgesic or addictive properties (Ref. 1). With usual antitussive doses, no effect has been noted on respiration, the cardiovascular system, or the gastrointestinal tract. With very large doses such as occur in drug abuse or accidental poisoning, respiratory depression has been noted (Refs. 2 and 3). However, no fatalities have been reported, even with doses in excess of 100 times the normal adult dose. Abuse has been reported by Degkwitz (Ref. 4) with doses of 300 to 1,500 mg several times daily, resulting in intoxication with bizarre behavior but no physical dependence.

(2) *Effectiveness.* Dextromethorphan is an active antitussive comparable to codeine on a mg-for-mg basis for cough suppression. Studies involving many species of animals and many methods for inducing cough have demonstrated that effectiveness of dextromethorphan as an antitussive is comparable to codeine (Refs. 5 through 7). Two studies (Refs. 8 and 9) reported that dextromethorphan was less effective than codeine in equivalent doses. It has been demonstrated that dextromethorphan, like codeine, acts through central (brain) inhibition of incoming cough stimuli (Refs. 10 and 11).

There have been a large number of studies in man over the past 20 years. These have consisted of: Experimentally induced cough with controlled double-blind crossover designs (Refs. 12 through 15) in which all but one (Ref. 13) showed effective antitussive activity; controlled subjective studies in pathologic cough (Refs. 13, 16 through 18); controlled objective studies in pathologic cough (Refs. 19 and 20); and uncontrolled subjective studies in a variety of disease states resulting in cough (Refs. 21 and 22).

The wide range of safety and low order of toxicity in clinical trials has been documented by Ralph (Ref. 21). The lack of addiction liability has been confirmed recently by Mansky and Jasinski (Ref. 23).

The majority of these clinical studies demonstrate effective antitussive activity. Even though a few of the studies questioned the effectiveness of dextromethorphan, the Panel concluded that based on the evidence presented, dextromethorphan is generally recognized as effective, and because of its low order of toxicity it is probably the safest antitussive presently available.

(3) *Dosage.* Adult oral dosage is 10 to 20 mg every 4 hours or 30 mg every 6 to 8 hours not to exceed 120 mg in 24 hours. Children 6 to under 12 years oral dosage is 5 to 10 mg every 4 hours or 15 mg every 6 to 8 hours not to exceed 60 mg in 24 hours. Children 2 to under 6 years oral dosage is 2.5 to 5 mg every 4 hours or 7.5 mg every 6 to 8 hours not to exceed 30 mg in 24 hours. For children under 2 years, there is no recommended dosage except under the advice and supervision of a physician.

(4) *Labeling.* The Panel recommends the Category I labeling for antitussive active ingredients. (See part III. paragraph B.1. below—Category I Labeling.) In addition, the Panel recommends the following specific labeling claims referrable to a central mechanism of action and its nonnarcotic designation: (i) *Indications.* (*a*) "Calms the cough control center and relieves coughing".

(*b*) "Non-narcotic cough suppressant for the temporary control of coughs".

(*c*) "Calms cough impulses without narcotics".

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c. *Diphenhydramine hydrochloride.* The Panel concludes that diphenhydramine hydrochloride is safe and effective for OTC use as an antitussive as specified in the dosage section discussed below.

(1) *Safety.* Diphenhydramine was the first of the antihistamines to be developed in the U.S. and was first used in 1946, clinically, for the relief of a wide variety of allergic symptoms. Diphenhydramine had a low order of toxicity in laboratory animals combined with a high degree of antihistaminic action. The Panel reviewed a number of studies contained in the submissions (Refs. 1 and 2) and concluded that with the exception of sedation, adverse effects have been rare and the drug is safe. The Panel has also found the drug to be safe for use

as an antihistamine and this use is discussed elsewhere in this document. (See part VII. paragraph B.1.c. below—Diphenhydramine hydrochloride.)

Clinical experience indicates that about 50 percent of persons have drowsiness as a side effect when 50 mg is given (Ref. 3). A double-blind controlled study in 20 males showed no evidence of interference with tests for memory, rotary pursuit, or reaction time with diphenhydramine hydrochloride in doses of 12.5 and 25 mg (Ref. 4). In a double-blind controlled subjective study on 546 patients with acute upper respiratory infection, drowsiness was reported in 11 of 269 patients receiving 25 mg diphenhydramine 4 times daily over a 3 day period (Ref. 5). Two of 277 patients receiving placebo also reported drowsiness. In infants, high doses of diphenhydramine may cause excitement and convulsions (Ref. 1). The acute toxicity of diphenhydramine in a variety of animal species is similar to other antihistamines such as pyribenzamine (Ref. 6). In children, 20 to 30 tables or capsules containing 50 mg each may represent a lethal or near lethal dose (Ref. 3).

The Panel has recommended specific warnings (see below) because an atropine-like effect is described by patients which includes a drying sensation of the mouth and nose and difficulty with urination in patients with enlarged prostates.

The Panel is aware that recently there was some concern expressed about the potential for misuse and abuse of diphenhydramine. This concern was contained in the statement of the Commissioner of Food and Drugs, which was included in the preamble to the report of the OTC Advisory Panel on Sedatives, Tranquilizers and Sleep-Aid Drug Products and published in the FEDERAL REGISTER of December 8, 1975 (40 FR 57292). This Panel will not attempt to comment on the findings of the other Panel or on the societal impact or abuse potential of diphenhydramine when used as an OTC nighttime sleep-aid. However, after a review of all the available data, the Panel concluded that diphenhydramine, as well as the other antihistamines reviewed, have a very low abuse potential and that there is little if any evidence of tolerance or habituation. However, the Panel does recognize that doses of diphenhydramine higher than those recommended for OTC use are likely to result in some side effects but that these side effects are sufficient to discourage abuse or misuse. In addition, the two pharmacologic groups for which this Panel is recommending diphenhydramine for OTC use, i.e., as an antitussive and as an antihistamine, are not recognized as being abusable by the drug abusing subculture. It should also be noted that diphenhydramine is available without a prescription for use as an antihistamine in Canada, the United Kingdom, and many other industralized countries of the world. The Panel was unable to determine that significant abuse of this ingredient was a problem in any of these countries.

The Panel concludes that diphenhydramine hydrochloride is safe for OTC use as an antitussive in the dosage ranges described below.

(2) *Effectiveness.* A number of animal studies employing chemical and mechanical methods for inducing cough (Refs. 7 through 9), including stimulation of the superior laryngeal nerve, the nerve that supplies the larynx and upper airway (Ref. 10), have demonstrated a reduction in cough frequency, which ranges from 25 percent to 120 percent of that produced by codeine depending on the species of animal employed and the method for inducing cough. The exact mechanism of action of diphenhydramine is not precisely known. However, because of its ability to inhibit the cough reflex resulting from stimulation of the superior laryngeal nerve, the Panel believes a central site of activity of diphenhydramine is a reasonable mode of action. Furthermore, the animal studies are cited as evidence that cough inhibition is not due to a general depression of the central nervous system but to a specific action, similar to codeine, on the "cough center".

Studies in man have consisted of: Experimentally induced cough employing a controlled double-blind crossover design in which both the 25 and 50 mg dose of diphenhydramine hydrochloride produced significant cough suppression equivalent to 15 mg of codeine (Refs. 11 through 13); two double-blind controlled objective studies in chronic cough, which showed antitussive activity for both 25 and 50 mg diphenhydramine hydrochloride as compared with placebo (Refs. 14 and 15), and the most common adverse reaction was drowsiness; controlled subjective study in chronic cough (Ref. 16) demonstrating antitussive activity superior to placebo but less than codeine; two subjective studies in acute upper respiratory infections, one controlled and one uncontrolled (Refs. 5 and 17), yielding equivocal results; and two objective cough counting studies in chronic cough, which were uncontrolled and showed a decrease in cough with all treatments (Refs. 18 and 19).

While drowsiness did not appear to be a major problem in the single dose studies, it is quite conceivable that repetitive doses may cause profound drowsiness in susceptible individuals. Furthermore, the drying effect of the drug's antihistaminic action could hinder bronchial drainage in patients with productive cough by making the secretions thicker and more difficult to expectorate.

(3) *Dosage.* Adult oral dosage is 25 mg every 4 hours not to exceed 150 mg in 24 hours. Children 6 to under 12 years oral dosage is 12.5 mg every 4 hours not to exceed 75 mg in 24 hours. Children 2 to under 6 years oral dosage is identified in the labeling section discussed below under professional labeling. For children under 2 years, there is no recommended dosage except under the advice and supervision of a physician.

(4) *Labeling.* The Panel recommends the Category I labeling for antitussive active ingredients. (See part III, paragraph B.1 below—Category I Labeling.) In addition, the Panel recommends the following specific labeling claims referable to a central mechanism of action and its nonnarcotic designation: (i) *Indications.* (*a*) "Calms the cough control center and relieves coughing".

(*b*) "Non-narcotic cough suppressant for the temporary control of coughs".

(*c*) "Calms cough impulses without narcotics".

(ii) *Warnings.* (a) "May cause marked drowsiness".

(*b*) "May cause excitability especially in children".

(*c*) "Do not take this product if you have glaucoma or have difficulty in urination due to enlargement of the prostate gland except under the advice and supervision of a physician".

(*d*) *"Caution.* Avoid driving a motor vehicle or operating heavy machinery".

(*e*) "Do not give this product to children under 6 years except under the advice and supervision of a physician".

(iii) *Professional labeling.* The Panel recommends that labeling provided to health professionals (but not to the general public) may contain the following additional dosage information: Children 2 to under 6 years oral dosage is 6.25 mg every 4 hours not to exceed 37.5 mg in 24 hours.

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Category I Labeling

The Panel recommends the following Category I labeling for antitussive active ingredients to be generally recognized as safe and effective and not misbranded as well as the specific labeling discussed in the individual ingredient statements:

a. *Indications.* (1) "Cough suppressant which temporarily reduces the impulse to cough".

(2) "For the temporary relief of cough due to minor throat and bronchial irritation as may occur with the common cold (cold) or with inhaled irritants".

(3) "Temporarily quiets coughing by its antitussive action".

(4) "Temporarily helps you cough less".

(5) "Temporarily helps to quiet the cough reflex that causes coughing".

b. *Warnings.* (1) "Do not give this product to children under 2 years except under the advice and supervision of a physician".

(2) "Do not take this product for persistent or chronic cough such as occurs with smoking, asthma, or emphysema, or where cough is accompanied by excessive secretions except under the advice and supervision of a physician".

(3) "*Caution:* A persistent cough may be a sign of serious condition. If cough persist for more than 1 week, tends to recur or is accompanied by high fever, rash or persistent headache, consult a physician".

2. *Category II conditions under which antitussive ingredients are not generally recognized as safe and effective or are misbranded.* The use of antitussives under the following conditions is unsupported by scientific data, and in some instances by sound theoretical reasoning. The Panel concludes that the following ingredients and labeling should be removed from the market until scientific testing supports their use.

Category II Active Ingredients

The Panel has classified the following antitussive active ingredients as not generally recognized as safe and effective or as misbranded:

Hydrocodone bitartrate (dihydrocodeinone)

Turpentine oil (spirits of turpentine) (oral)

a. *Hydrocodone bitartrate (dihydrocodeinone).* The Panel concludes that hydrocodone bitartrate (dihydrocodeinone) is safe for prescription use but that its addiction potential and other adverse reactions, including respiratory depression, are so serious that it is not appropriate for OTC use. The Panel concludes that the current prescription status of hydrocodone bitartrate under the Federal Controlled Substances Act is appropriate and that the ingredient should not be available as an OTC antitussive.

(1) *Safety.* Pharmacologically, hydrocodone is a more potent antitussive and analgesic than codeine and its adverse reactions, including addiction potential, are greater than codeine (Refs. 1 through 3). Depression of respiration has been noted in animals (Ref. 4) and man (Ref. 5). The addiction problem, which approaches that of the more potent narcotics such as morphine, has been reviewed by Rosenwald and Russell (Ref. 6). Because its potency as a narcotic falls between morphine and codeine, respiratory depression can be a real hazard with hydrocodone, especially in patients with chronic obstructive pulmonary disease.

(2) *Effectiveness.* Hydrocodone is an active antitussive with a potency approximately three times that of codeine on a weight basis.

A number of uncontrolled clinical trials (Refs. 7 through 10) suggest effective antitussive activity in chronic lung disease, including pulmonary tuberculosis lasting for 8 to 12 hours. A subsequent double-blind clinical trial (Ref. 11) and experimental cough-challenge study (Ref. 12) confirmed its antitussive activity.

(3) *Evaluation.* The Panel concludes that the activity of hydrocodone bitartrate in chronic and serious diseases make it a valuable drug for use under proper medical supervision and for that reason recommends that its availability continue to be restricted to prescription use only, under the Federal Controlled Substances Act.

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b. *Turpentine oil (spirits of turpentine) (oral).* The Panel concludes that oil of turpentine is not safe for OTC use when taken orally as an antitussive.

(1) *Safety.* Oil of turpentine is a volatile oil distilled from turpentine, an oleoresin obtained from the pine tree. It has a characteristic odor and taste. The substance has been administered orally, topically, and by inhalation.

In doses of 15 ml in children and 150 ml in adults fatal poisoning may occur (Ref. 1). Excessive oral doses produce marked irritation of the alimentary tract, especially of the stomach and of the pelvic organs. Toxic symptoms include vomiting, diarrhea, acute pain, renal irritation, bloody stools and hyperemia of all abdominal organs. Continued use may lead to cloudy swelling and fatty degeneration of the liver. Abnormal central nervous system symptoms may develop (Refs. 2 and 3).

Since no safe oral dose has been established for effective use as an antitussive, the Panel concludes that turpentine oil should not be available for oral OTC use as an antitussive. However, elsewhere in this document, the Panel concludes that the ingredient is safe when applied topically or used as an inhalant but that there are insufficient data to permit final classification of its effectiveness for inhalant or topical use as an antitussive. (See part III. paragraph B.3.1. below—Turpentine oil (spirits of turpentine) (topical/inhalant).)

(2) *Effectiveness.* Oil of turpentine is irritating and its chief suggested uses are based on this property (Refs. 1 and 4). There is no evidence to support its effectiveness as an antitussive when taken orally.

(3) *Evaluation.* The Panel is unable to determine a safe oral dose for turpentine oil for use as an antitussive. The Panel is of the opinion that the risk from oral administration outweighs whatever benefit might occur. Therefore, the Panel concludes that turpentine oil is not safe for oral use as an antitussive.

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Category II Labeling

The Panel concludes that the use of certain labeling claims related to the safety and/or effectiveness of the product is unsupported by scientific data, and in some instances by sound theoretical reasoning. The Panel has previously discussed such labeling. (See part II. paragraph O. above—CCABA Product Labeling Claims Not Supported by Scientific Evidence.) However, labeling that is descriptive of the product such as its taste or appearance is acceptable.

Unacceptable claims for antitussives include any statement containing the term chest or lung congestion. The term "congestion", which may be interpreted by the target population to denote a discomfort of the chest, may result from a variety of causes, several of which may be of a most serious nature and require professional attention.

All claims that state or imply a therapeutic action or safety property peculiar to the preparation that cannot be demonstrated in controlled studies are not acceptable, e.g., "specially formulated", "improved", or "selected", "natural", "extra strength", "teamed components", "superior to ordinary", "modern", and "superior".

Statements alluding to greater potency, such as "extra strength" or "contains more antitussive per dose" are misleading because there are no acceptable controlled studies documenting that one preparation is more potent than another, particularly for Category I drugs. There is also no justification for claiming more antitussive per dose because there is no scientific merit from a therapeutic point of view between 15 mg of drug A and 30 mg of drug B if they are both effective. Therefore, any claim for "extra strength" or "higher dose level" may be misleading in that the product is no more effective and in fact may increase the potential for side effects. Under such circumstances the Panel feels that all such claims are misleading to the consumer.

Claims implying a physiological effect that either has no foundation or meaning will be meaningless to the public are unacceptable; such as, "gets to the roots of", "recommended by doctors", "travels through the blood stream", "works internally".

Claims for relief where time is indeterminate and not supported by scientific data are unacceptable; such as, "fast" and "prompt".

Statements such as "a dramatic advance", "the greatest advance in cough relief", "the modern way to stop coughs" etc., are vague generalizations, which imply a superiority of a product. These statements cannot be supported by scientific evidence, and since they are meaningless, can only have the effect of misleading the consumer.

The Panel concludes that such labeling should be removed from the market until scientific testing supports their use.

3. *Category III conditions for which the available data are insufficient to permit final classification at this time.* The Panel concludes adequate and reliable scientific evidence is not available at this time to permit final classification of the claimed ingredients and conditions listed below. The Panel believes it reasonable to provide 4 years for the development and review of such evidence. Marketing need not cease during this time if adequate testing is undertaken. If adequate effectiveness data are not obtained within 4 years, however, the ingredients and conditions listed in this category should no longer be marketed in over-the-counter products. Effectiveness as an antitussive must be demonstrated by controlled objective studies employing cough-counting techniques. Subjective data, alone, are unacceptable because of the marked variability in the subjective awareness of cough. Studies have shown (Refs. 1 and 2) that there is a poor correlation in the subjective appraisal of the effectiveness of the cough suppressant and the actual objective studies done by employing cough-counting techniques.

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Category III Active Ingredients

The Panel concludes that the available data are insufficient to permit final classification of the following claimed antitussive active ingredients:

Beechwood creosote
Camphor (topical/inhalant)
Caramiphen edisylate (caramiphen ethanedisulfonate)
Carbetapentane citrate
Cod liver oil
Elm bark
Ethylmorphine hydrochloride
Eucalyptol/eucalyptus oil (topical/inhalant)
Horehound (horehound fluidextract)
Menthol/peppermint oil (topical/inhalant)
Noscapine (noscapine hydrochloride)
Thymol (topical/inhalant)
Turpentine oil (spirits of turpentine) (topical/inhalant)

a. *Beechwood creosote.* The Panel concludes that beechwood creosote is safe in the dosage range used as an antitussive, but there are insufficient data to permit final classification of its effectiveness for OTC use as an antitussive.

(1) *Safety.* Clinical experience has confirmed that beechwood creosote in the usual doses contained in lozenges or cough mixtures for antitussive activity is safe.

Creosote is a distillate of wood tar and has a smokey color and a pungent taste. Dosages in excess of 4 gm 3 times daily produce giddiness, dimness of vision, circulatory collapse, convulsions and coma (Ref. 1). Because of the taste, it is normally given well-diluted (Ref. 2). Occasional adverse gastrointestinal side effects are mentioned in one report but are poorly documented (Ref. 3). Based on the available data and the presence of beechwood creosote on the market for many years, the Panel concludes that this ingredient is safe for OTC use.

(2) *Effectiveness.* There are no well-controlled objective studies documenting the effectiveness of beechwood creosote, alone, as an antitussive. Only one submission to the Panel (Ref. 4), reports a double-blind controlled study, for a combination product containing creosote, in 25 patients with chronic cough employing cough-counting techniques, which is said to show transient drug activity with statistical significance at 1 hour after drug administration. The statistical analysis and methodology is cumbersome and confusing. It is unclear whether a significant difference from the placebo was obtained. Because the dose of the product is unstated there is a lack of information regarding the smoking habits of the subjects in this study, and no evidence to indicate that the high speed, automatic electronic counter is accurate and reliable by comparing it with actual cough counts, serious questions are raised by the Panel about the acceptability of this study.

According to the standard compendia (Refs. 1 and 5), an average dose of beechwood creosote is 250 mg 3 or 4 times daily. In the two submissions to the panel listing of creosote, the dosages are 3.29 mg/lozenge and 33 mg/15 ml every 3 hours (Ref. 6). This 40 to 80 fold differ-

ence in dose (3.29 mg/lozenge, 8 doses/daily) appears illogical, and there is no evidence to indicate that creosote is effective in such low doses. The Panel concludes that further studies are needed to determine effectiveness.

(3) *Proposed dosage.* Adult oral dosage is 250 mg every 4 to 6 hours not to exceed 1500 mg in 24 hours. Children 6 to under 12 years oral dosage is 125 mg every 4 to 6 hours not to exceed 750 mg in 24 hours. Children 2 to under 6 years oral dosage is 62.5 mg every 4 to 6 hours not to exceed 375 mg in 24 hours. For children under 2 years, there is no recommended dosage except under the advice and supervision of a physician.

(4) *Labeling.* The Panel recommends the Category I labeling for antitussive active ingredients. (See part IV. paragraph B.1. above—Category I Labeling.)

(5) *Evaluation.* Data to demonstrate effectiveness as an antitussive will be required in accordance with the guidelines set forth below for testing antitussive drugs. (See part IV. paragraph C. below—Data Required for Evaluation.)

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(4) OTC Volume 040289.

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b. *Camphor (topical/inhalant).* The Panel concludes that camphor is safe in the dosage ranges used when applied topically or as an inhalant, but there are insufficient data to permit final classification of its effectiveness for topical or inhalant OTC use as an antitussive.

(1) *Safety.* Clinical experience has confirmed that camphor (topical/inhalant) is safe in the dose ranges used as an antitussive.

Camphor is a local irritant producing skin redness when rubbed on the skin. However, when not vigorously applied, it may produce a feeling of coolness on the skin as does menthol. It acts similarly on the respiratory tract. Taken orally in small doses it produces a feeling of warmth and comfort in the stomach, but in larger doses it is irritating and can cause nausea and vomiting. Camphor also has a mild local anesthetic action, and its application to the skin may be followed by numbness. The systemic effects are primarily related to stimulation of the central nervous system. The ingestion of solid camphor by children can cause convulsions (Ref. 1). As little as 0.75 gm of camphor (equivalent to a teaspoonful of liniment of camphor or camphorated oil, which contain 20 percent camphor) has been fatal to a child. Commercially available ointments containing mixtures of volatile substances for use as decongestants or antitussives contain about 5 percent camphor. Since it is conceivable that ingestion of a sufficient amount of such a preparation could produce toxic effects in a young child, a suitable warning should be present on the label. The ingestion of 2 gm of camphor generally produces toxic effects in an adult, although up to 45 gm has been ingested with recovery (Ref. 2).

(2) *Effectiveness.* There are no well-controlled studies documenting the effectiveness of camphor (topical/inhalant) as an antitussive. Its effectiveness is uncertain due to lack of properly controlled studies of the substance by itself.

Studies involving objective measurement of antitussive activity of camphor primarily involve mixtures of volatile substances topically applied as ointments (Refs. 3 and 4), as steam inhalations (Refs. 5 through 7), and as lozenges (Refs. 8 and 9), evaluated against artificially induced cough in normal subjects by the citric acid aerosol method. In these studies, significant antitussive activity is demonstrated for a mixture of volatile substances containing camphor compared to placebo, but the contribution of the camphor component to this effect is not evident. In a crossover study involving 16 subjects, the effects of 5.3 percent camphor in a petrolatum ointment applied to the chests of subjects were compared to an ointment containing several volatile substances including 5.3 percent camphor and to a placebo (petrolatum) in suppressing a citric acid aerosol-induced cough. The combination ointment containing camphor induced a significant decrease in cough counts at all challenge times from ½ hour through 2 hours averaging about 20 percent decrease in cough counts at the ½- and 1-hour intervals, whereas the single ingredient camphor ointment yielded a significant decrease in cough counts just at the ½- and 1-hour intervals averaging about 10 percent reduction, and the petrolatum yielded no significant difference in cough counts compared with base line (Ref. 3).

(3) *Proposed dosage.* Dosage for adults and children 2 to under 12 years is as follows: (i) For topical use as a 5 percent ointment preparation: To be rubbed on the throat, chest, and back as a thick layer. The area of application may be covered. However, clothing should be left loose about the throat and chest to help the vapors rise to reach the nose and mouth. Applications may be repeated up to 3 times daily.

(ii) For steam inhalation use as a 7 percent solution: 1 tablespoonful of solution per quart of water is added directly to the water in a hot steam vaporizer, bowl or wash basin; or 2 teaspoonfuls of solution per pint of water are added to an open container of boiling water. Breathe in vapors during the period of medicated steam generation. May be repeated 3 times daily.

(iii) For topical use as a lozenge 0.02 to 15 mg: Allow lozenge to dissolve slowly in mouth. May be repeated every ½ to 1 hour.

For children under 2 years, there is no recommended topical or inhalant dosage except under the advice and supervision of a physician.

(4) *Labeling.* The Panel recommends the Category I labeling for antitussive active ingredients. (See part III. paragraph B.1. above—Category I Labeling.) In addition, the Panel recommends the following specific labeling: (i) For topical ointment use: *Warning:* "For external use only. Do not take by mouth or place in nostrils".

(ii) For steam inhalation use: *Warning:* "For steam inhalation only. Do not take by mouth".

(5) *Evaluation.* The Panel made the following recommendations:

(i) For topical ointment use: Data to demonstrate effectiveness will require only one additional controlled cough-counting objective study in patients with coughs due to respiratory disease in accordance with the guidelines set forth below for testing antitussive drugs. (See part III. paragraph C. below—Data Required for Evaluation.)

(ii) For steam inhalation use: Data to demonstrate effectiveness will be required in accordance with the guidelines set forth below for testing antitussive drugs. (See part III. paragraph C. below—Data Required for Evaluation.)

(iii) For topical use as a lozenge: Data to demonstrate effectiveness will be required in accordance with the guidelines set forth below for testing antitussive drugs. (See part III. paragraph C. below—Data Required for Evaluation.)

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c. *Caramiphen edisylate (caramiphen ethanedisulfonate).* The Panel concludes that caramiphen edisylate is safe but there are insufficient data to permit final determination of its effectiveness for OTC use as an antitussive.

(1) *Safety.* Clinical experience has confirmed that caramiphen edisylate is safe in the dose ranges used as an antitussive. Acute and chronic toxicity studies in animals indicate a wide margin of safety, and caramiphen was judged to be considerably less toxic than codeine (Ref. 1). Instances of dizziness and drowsiness have been reported with dosage levels of 10 mg of caramiphen edisylate 3 times daily (Ref. 2). The incidence of these mild reactions increased when the dose was doubled, and one patient experienced a transient period of disorientation (Ref. 2). In a number of clinical trials, 12 of 172 patients reported adverse reactions, 4 of which were probably not drug related (Ref. 3). Although caramiphen pharmacologically is anticholinergic, with ½ to 1/10 the drying (antisecretory) effects of atropine, there have been no reports concerning its effect on bronchial secretions and no difficulty with retained secretions (Ref. 4).

At the average dose of 10 to 20 mg 3 to 4 times daily, few toxic reactions have been reported. Reported side effects have included slight nausea, dizziness, and occasional drowsiness, which appeared to be dose related. Until additional experience has accumulated, the labeling warning below concerning glaucoma and enlarged prostate, which may cause a block to the flow of urine, is deemed necessary in view of the drug's anticholinergic properties (Ref. 4).

(2) *Effectiveness.* There are no well-controlled objective, clinical studies documenting the effectiveness of caramiphen edisylate as an antitussive.

Studies in animals indicate that caramiphen is a centrally acting antitussive (Refs. 1 and 5). Cough suppression is due to an increase in the central threshold for cough. Almost all of the reports of studies are uncontrolled, subjective clinical trials (Refs. 6 and 7). Two controlled studies with induced cough showed 10 mg caramiphen to be singificantly superior to placebo but slightly less active than codeine 15 mg (Refs. 8 and 9). The only well-controlled crossover study was performed by Abelmann, Gaensler and Badger (Ref. 2), who concluded that caramiphen was superior to placebo but not as effective as codeine or dihydrocodeinone as a cough suppressant by subjective criteria, and that it decreased the amount of sputum in 61 percent of patients but without evidence of retention of secretions.

A controlled cough-counting study was recently reported in 25 patients with chronic cough (Ref. 10). The results of this study failed to show the efficacy of a single dose of 20 mg caramiphen as compared with placebo, but offered to show a significant antitussive effect after the fourth and fifth doses of the drug. Because of a lack of information regarding the smoking habits of the subjects in this study, and no evidence to indicate that the high speed, automatic electronic counter is accurate and reliable by comparing it with actual cough counts, serious questions about the acceptability of this study are raised.

(3) *Proposed dosage.* Adult oral dosage is 10 to 20 mg every 4 to 6 hours not to exceed 80 mg in 24 hours. Children 6 to under 12 years oral dosage is 5 to 10 mg every 4 to 6 hours not to exceed 40 mg in 24 hours. Children 2 to under 6 years oral dosage is 2.5 to 5 mg every 4 to 6 hours not to exceed 20 mg in 24 hours. For children under 2 years, there is no recommended dosage except under the advice and supervision of a physician.

(4) *Labeling.* The Panel recommends the Category I labeling for antitussive active ingredients. (See part III. paragraph B.1. above—Category I Labeling.) In addition, the Panel recommends the following specific claims referrable to a central mechanism of action and its nonnarcotic designation: (i) *Indications.* (*a*) "Calms the cough control center and relieves coughing".

(*b*) "Non-narcotic cough suppressant for the temporary control of coughs".

(*c*) "Calms cough impulses without narcotics".

(ii) *Warnings.* (*a*) "Do not take this product if you have glaucoma or have difficulty in urination due to an enlarged prostate gland except under the advice and supervision of a physician".

(*b*) *"Caution:* Do not give this product to children taking other drugs except under the advice and supervision of a physician".

(5) *Evaluation.* Data to demonstrate effectiveness will be required from only one additional well-controlled cough-counting objective study in patients with cough due to respiratory disease in accordance with the guidelines set forth below for testing antitussive drugs. (See part III. paragraph C. below—Data Required for Evaluation.)

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d. *Carbetapentane citrate.* The Panel concludes that carbetapentane citrate is safe but there are insufficient data to permit final determination of its effectiveness for OTC use as an antitussive.

(1) *Safety.* Clinical experience has confirmed that carbetapentane citrate is safe in the dose range used as an antitussive.

Studies in several animal species revealed a low order of toxicity, which was comparable to codeine phosphate (Ref. 1). Intravenous administration resulted in slight transient falls in blood pressure with no effect on respiration. In addition, carbetapentane possesses marked antispasmodic (relieves spasms) activity with weak anticholinergic (atropine-like) and local anesthetic properties. Adverse reactions in humans consisted for the most part of mild dryness of the mouth (Ref. 2). In this study, nine of 31 patients reported this side effect. An additional patient complained of severe nausea and loss of appetite and discontinued medication.

At an average dose of 25 mg 4 times daily, few side effects have been reported, and have consisted mostly of dryness of the mouth. On the whole, this atropine-like effect was mild and did not interfere with sputum production (Ref. 3), but the labeling warning (see below) concerning glaucoma and enlarged prostate is deemed necessary because of the anticholinergic properties of carbetapentane.

(2) *Effectiveness.* There are no well-controlled studies documenting the effectiveness of carbetapentane citrate as an antitussive.

Animal studies employing a variety of methods for experimentally inducing cough as well as pathologic cough in dogs indicate that the onset of action and duration of cough suppression is equivalent to codeine (Refs. 1 and 4), but in a review of the literature (Ref. 5) there was considerable disagreement as to carbetapentane's relative antitussive potency as compared with codeine. Clinical studies were all subjective in type and only one had a placebo control (Ref. 6). At doses ranging between 7 and 25 mg 3 to 4 times daily, most investigators have reported "good" to "excellent" antitussive effect. Many of the clinical trials were of short duration in acute respiratory conditions and were uncontrolled (Refs. 3, and 7 through 9). The Council on Drugs of the American Medical Association has stated that, "available clinical evidence suggests that the effectiveness of the drug is limited to the acute (short duration) type of cough. Further and better controlled observations are

needed to establish its clinical usefulness" (Ref. 10). However, other investigators (Refs. 5, 11, and 12) have found carbetapentane to be effective in all types of cough. In one study, carbetapentane was not as effective as codeine for severe (intense and frequent) cough (Ref. 13). None of these clinical studies employed objective cough-counting techniques and few were adequately controlled.

(3) *Proposed dosage.* Adult oral dosage is 15 to 30 mg every 4 to 6 hours not to exceed 180 mg in 24 hours. Children 6 to under 12 years oral dosage is 7.5 to 15 mg every 4 to 6 hours not to exceed 90 mg in 24 hours. Children 2 to under 6 years oral dosage is 3.75 to 7.5 mg every 4 hours not to exceed 45 mg in 24 hours. For children under 2 years, there is no recommended dosage except under the advice and supervision of a physician.

(4) *Labeling.* The Panel recommends the Category I labeling for antitussive active ingredients. (See part III. paragraph B.1. above—Category I Labeling.) In addition, the Panel recommends the following specific claims referable to a central mechanism of action and its nonnarcotic designation: (i) *Indications.* (*a*) "Calms the cough control center and relieves coughing".

(*b*) "Non-narcotic cough suppressant for the temporary control of coughs".

(*c*) "Calms cough impulses without narcotics".

(ii) *Warnings.* (*a*) "Do not take this product if you have glaucoma or have difficulty in urination due to an enlarged prostate gland except under the advice and supervision of a physician".

(*b*) "Do not give this product to children under 2 years except under the advice and supervision of a physician".

(*c*) *"Caution:* Do not give this product to children taking other drugs except under the advice and supervision of a physician".

(5) *Evaluation:* Data to demonstrate effectiveness will be required in accordance with the guidelines set forth below for testing antitussive drugs. (See part III. paragraph C. below—Data Required for Evaluation.)

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(13) Letter to Dumas, K. from S. Katz is included in OTC Volume 040298.

e. *Cod liver oil.* The Panel concludes that cod liver oil is safe but there are insufficient data to determine its effectiveness for OTC use as an antitussive.

(1) *Safety.* Clinical experience has confirmed that cod liver oil is safe in the dose ranges used as an antitussive. Clinical experience over more than 100 years of use has demonstrated that cod liver oil is safe, and no significant evidence of toxicity has been reported when used in a wide variety of disease states as well as for vitamin supplementation. Rare instances of hypervitaminosis with resulting nausea, vomiting, and diarrhea have been reported with excessive doses (Ref. 1).

(2) *Effectiveness.* There are no well-controlled studies documenting the effectiveness of cod liver oil as an antitussive. Except for a brief statement that cod liver oil is also given with benefit in "respiratory catarrhs" in subacute and chronic bronchitis, "catarrhal pneumonia," and frequent and persistent "colds" in children and the aged (Ref. 1), there is no actual reference to its value as a cough suppressant. In fact, all of the available references state that the value of cod liver oil in therapeutics lies in its high content of vitamins A and D (Refs. 2 and 3).

(3) *Proposed dosage.* The usual dosage is said to be 5 ml (1 teaspoon), which contains no less than 3,900 USP units of vitamin A and 386 USP units of vitamin D which provides the daily requirements for children and adults of both these vitamins (Refs. 3 and 4). The dosage of an emulsion containing 50 percent cod liver oil is 15 ml or 1 tablespoon (Ref. 2). However, all of these dosage forms refer to its use as a vitamin supplement.

The Panel is aware of one reference to a dosage of 2 teaspoons after each meal in convalescence from respiratory diseases. The duration of therapy is not stated (Ref. 2). The Panel concludes that the pharmaceutical industry should consult with the Food and Drug Administration as to a suitable proposed dosage for testing. Otherwise, the Panel recommends that each drug manufacturer evaluate the dosage as labeled on the manufacturer's marketed product(s).

(4) *Labeling.* The Panel recommends the Category I labeling for antitussive active ingredients. (See part III. paragraph B.1. above—Category I Labeling.)

(5) *Evaluation.* Data to demonstrate effectiveness will be required in accordance with the guidelines set forth below for testing antitussive drugs. (See part III. paragraph C. below—Data Required for Evaluation.)

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(4) "The United States Dispensatory," 27th Ed., Edited by Osol, A. and R. Pratt, J. B. Lippincott Co., Philadelphia, p. 332, 1973.

f. *Elm Bark.* The Panel concludes that elm bark (slippery elm, ulmus rubra) is safe but there are insufficient data to determine its effectiveness for OTC use as an antitussive.

(1) *Safety.* Clinical experience has confirmed that elm bark is safe in the dose ranges used as an antitussive. Clinical experience over a period of several hundred years has yielded no evidence of toxicity when used either as a lozenge, infusion for internal consumption, or as a poultice applied to the skin for antitussive action.

(2) *Effectiveness.* There are no well-controlled studies documenting the effectiveness of elm bark as an antitussive. Elm bark was used by the Indians and early settlers of North America in the form of poultices and liquids for the treatment of fevers and colds with cough. It is referred to by Schopf in 1787 as "salve bark" (Ref. 1). The mucilaginous quality of these preparations is said to confer excellent protective demulcent properties, which were employed in the form of lozenges to relieve irritation of the pharynx (Ref. 2).

(3) *Proposed dosage.* The Panel is unable to determine a proposed dosage. Troches or lozenges of slippery elm are listed as containing 0.2 gm of elm per troche with the dosage being one troche, and the frequency of administration is given as "ad libitum" (Ref. 3). A warm infusion was prepared by stirring 1 oz of the powdered bark in a pint of hot water, which was then taken "ad libitum" (Ref. 2). The Panel concludes that the pharmaceutical industry should consult with the Food and Drug Administration as to a suitable proposed dosage for testing. Otherwise, the Panel recommends

that each drug manufacturer evaluate the dosage as labeled on the manufacturer's marketed product(s).

(4) *Labeling.* The Panel recommends the Category I labeling for antitussive active ingredients. (See paragraph III. paragraph B.1. above—Category I Labeling.)

(5) *Evaluation.* Data to demonstrate effectiveness will be required in accordance with the guidelines set forth below for testing antitussive drugs. (See part III. paragraph C. below—Data Required for Evaluation.)

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g. *Ethylmorphine hydrochloride.* The Panel concludes that ethylmorphine hydrochloride is safe but there are insufficient data to permit final determination of its effectiveness for OTC use as an antitussive.

(1) *Safety.* Clinical experience has confirmed that ethylmorphine hydrochloride is safe in the dose range used as an antitussive.

There are few well-documented studies in animals and man defining the incidence of adverse reactions. Ethylmorphine is the ethyl ether of morphine and its pharmacologic properties are similar to codeine, the methyl ether of morphine. Tolerance and physical dependence have been reported after prolonged use of ethylmorphine (Ref. 1). Other adverse reactions, such as constipation and respiratory depression, are similar to those of codeine. Topically, ethylmorphine is an irritant to mucous membranes and causes an inflammatory reaction with increased secretion of mucus (Ref. 2).

(2) *Effectiveness.* There are no well-controlled studies documenting the effectiveness of ethylmorphine as an antitussive.

Animal studies employing induced cough showed ethylmorphine to have some antitussive activity (Refs. 3 and 4).

Since the early 1900's, ethylmorphine has been used clinically at approximately the same dosage level as codeine. Because of its failure to demonstrate any advantage over codeine, it never attained the popularity of codeine as an antitussive (Ref. 5), and hence there are few studies demonstrating its use as an antitussive. Only one paper reported that ethylmorphine in a dose of 15 to 22.5 mg was as effective as 30 to 60 mg of codeine in suppressing cough due to tuberculosis (Ref. 6). Unlike codeine, there are no objective clinical trials or well-controlled subjective studies in the literature.

Dosage range and pharmacologic activity, including adverse reactions and abuse potential, are similar to codeine. While ethylmorphine is regulated under the Federal Controlled Substances Act, it has not been tested at the Addiction Research Center, Lexington, KY because of its infrequent use (Ref. 5).

(3) *Proposed dosage.* Adult oral dosage is 15 mg every 4 to 6 hours not to exceed 90 mg in 24 hours. Children 6 to under 12 years oral dosage is 7.5 mg every 4 to 6 hours not to exceed 45 mg in 24 hours. Children 2 to under 6 years oral dosage is 3.75 mg every 4 to 6 hours not to exceed 22.5 mg in 24 hours. For children under 2 years, there is no recommended dosage except under the advice and supervision of a physician.

(4) *Labeling.* The Panel recommends the labeling for Category I antitussive active ingredients. (See part III. paragraph B.1. above—Category I Labeling.) In addition, the Panel recommends the following specific claims referrable to its central mechanism of action: (i) *Indications.* "Calms the cough control center and relieves coughing".

(ii) *Warnings.* (*a*) "May cause or aggravate constipation".

(*b*) "Do not give this product to children taking other drugs except under the advice and supervision of a physician".

(*c*) "Do not take this product if you have a chronic pulmonary disease or shortness of breath except under the advice and supervision of a physician".

(5) *Evaluation:* Data to demonstrate effectiveness will be required in accordance with the guidelines set forth below for testing antitussive drugs. (See part III. paragraph C. below—Data Required for Evaluation.)

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h. *Eucalyptol/eucalyptus oil (topical/inhalant).* The Panel concludes that eucalyptol/eucalyptus oil is safe in the dosage ranges used when applied topically or as an inhalant but there are insufficient data to permit final classification of its effectiveness for topical or inhalant OTC use as an antitussive.

(1) *Safety.* Clinical experience has confirmed that eucalyptol/eucalyptus oil (topical/inhalant) is safe in the dose ranges used as an antitussive.

Eucalyptus oil is about 70 percent active eucalyptol. Fatalities have followed doses of the oil as small as 3.5 ml, although recovery has occurred after doses of 20 and even 30 ml. Symptoms include epigastric burning with nausea and vomiting, vertigo, ataxia, muscle weakness and stupor (Refs. 1 and 2). A study of 223 subjects in which an ointment containing several volatile substances, including eucalyptus oil 1.3 percent, was applied for 48 hours to areas of intact skin under a patch and to abraded skin, revealed no instances of irritation, inflammation, wheal or hives following the period of exposure (Ref. 3). A study of 10 subjects who received application of an ointment containing several volatile substances, including eucalyptus oil 1.3 percent, to their trunks 3 times daily for 3 weeks, then 1 week off followed by another 1 week of treatment, revealed no local reactions during this subsequent challenge phase (Ref. 4). A study of infants and children with respiratory infection who received an ointment containing a mixture of volatile oils, including eucalyptus oil 1.3 percent, applied to the chest and neck demonstrated no adverse effect from inhaled vapors by that route of administration on the rate of clearing of laryngeal edema (Ref. 5).

Vapors are also produced by placing a liquid mixture of volatile substances, including eucalyptus oil 1.7 percent, in the water of a hot steam vaporizer and administered via inhalation. Exaggerated-use studies in adults and children, i.e., exposure for several hours to higher than recommended exposure concentrations of these vapors either due to sitting in closer proximity to the vaporizer or placing two to five times the recommended dose of the volatile substance in the vaporizer, were not associated with irritating or toxic effects (Refs. 6 and 7).

A series of studies assessing buccal safety and overt side effects from lozenges containing a mixture of volatile oils was conducted in over 300 subjects (Refs. 8 through 11). Lozenges containing up to 5.5 mg eucalyptus oil were dissolved in the mouth every hour for 8 hours on 2 successive days. Mild erythema of the buccal mucosa and tongue was observed but did not differ appreciably from the response to dissolving lozenge sugar base without volatile oils. The incidence of gastrointestinal symptoms did not differ from control either (Refs. 8 through 11).

An aerosolized dosage form of volatile substances including 1 percent eucalyptus oil has also been utilized for treatment of nasal congestion. In humans, such aerosol sprays have been generally safe when used as directed, but there have been reports of deaths from deliberate sniffing abuse, particularly when the subject inhales from a plastic bag into which the material has been sprayed (Ref. 12). Furthermore, one commercial preparation containing a particular solvent (1,1,1-trichloroethane) was recently

recalled from the market due to potential hazards of this substance (Ref. 13).

(2) *Effectiveness.* There are no well-controlled studies documenting the effectiveness of ecualyptol/eucalyptus oil (topical/inhalant) as an antitussive. Its effectiveness is uncertain due to lack of properly controlled studies of the substance by itself.

Eucalyptus oil is a component of a number of currently marketed OTC topically applied preparations utilized as antitussives, e.g., ointments, steam inhalation, and lozenges. In a crossover study involving 16 subjects, the effects of a 1.3 percent eucalyptus oil in petrolatum ointment applied to the chests of the subjects was compared to an ointment containing several volatile substances, including 1.3 percent eucalyptus oil, and to petrolatum in suppressing a citric acid aerosol induced cough. The combination ointment containing eucalyptus oil induced a significant decrease in cough counts at all challenge times from ½ hour through 2 hours averaging about 20 percent decrease at the ½ and 1 hour intervals, whereas the single ingredient eucalyptus oil ointment yielded a significant decrease in cough counts at the ½ hour through 1 and ½ hour intervals averaging about 15 to 18 percent reduction at these times, and the petrolatum yielded no significant decrease in cough counts compared with base line (Ref. 14). Similar results with a combination ointment containing 1.3 percent eucalyptus oil were obtained in two additional induced cough studies conducted by the same investigator (Refs. 14 and 15).

A single-blind crossover cough counting study of 27 patients exhibiting stabilized chronic cough, utilized twice daily chest application of either the ointment containing several volatile substances an ointment containing several volatile oils including 1.3 percent eucalyptus oil or a placebo (petrolatum base). Neither the ointment mixture of volatile substances nor the eucalyptus oil ointment induced a significant decrease in cough counts compared to placebo after the morning application, but a significant 20 percent cough count reduction compared to placebo was obtained following the afternoon dose of the ointment mixture. An average reduction in cough counts of about 10 percent compared to placebo was noted following the afternoon dose of eucalyptus oil ointment but this was not statistically significant (Ref. 16).

A liquid mixture of volatile substances was evaluated. The mixture was added to water of a hot steam vaporizer and administered via inhalation, and contains menthol 3.66 percent, camphor 7 percent, eucalyptus oil 1.7 percent and tincture of benzoin 5 percent. Three crossover studies compared the effects of this volatile substance containing liquid in steam (1 tablespoonful per quart of water) to steam alone in suppressing coughs artificially induced by the citric acid aerosol technique. In each case, both steam and medicated steam induced a statistically significant reduction in cough counts during the period of administration. In two of the studies the cough reduction with the medicated steam was statistically greater than with steam alone and persisted beyond the period of actual administration to the subjects (Refs. 17 through 19). In an objective cough counting study on patients with acute upper respiratory disease, the medicated steam showed significantly lower cough counts than the unmedicated steam for the 4 hours the patients were exposed to vaporization, and for 2 additional hours after vaporizer therapy was discontinued (Ref. 20). Subjective evaluation studies of adults and infants with cough associated with respiratory infection demonstrated statistically significant antitussive effectiveness of both the volatile substances in steam (1 tablespoon per quart) and of steam alone. In some of these studies the effect of the medicated steam was judged statistically superior to the steam alone (Refs. 21 and 22).

The variety of lozenge preparations containing a mixture of volatile substances that include eucalyptus oil have been studied for their ability to suppress citric acid aerosol induced cough in normal subjects. Since each of these lozenge preparations contain different concentrations of eucalyptus oil and other volatile substances, the study results will be individually summarized. The general study format involved a single blinded crossover design in which a group of cough standardized normal subjects were tested with each of two lozenge formulations, i.e., the active formulation and its vehicle control against cough artificially induced by the citric acid aerosol technique.

Two studies involving a total of 40 subjects used similar active formulations consisting of menthol 9.6 mg and eucalyptus oil 5.5 mg per lozenge. In these studies the active formulation produced significant cough reductions at the 10 to 40 minute challenge periods, reaching a peak of 25 to 35 percent reduction at the 10 and 20 minute intervals, whereas the control lozenge produced a significant reduction, 10 to 15 percent maximum, at only the 10 minute challenge (Refs. 23 and 24). In a study of 9 subjects receiving a two lozenge dose of menthol (1.0 mg/lozenges) and eucalyptol (7.6 mg/lozenge) elevated citric acid thresholds of 130 to 146 percent of control for 3 to 5 hours after dosing were obtained, although a placebo control lozenge was not utilized in this study for comparison (Ref. 25). Another study of 20 subjects utilizing a formulation of menthol 2.78 mg, eucalyptus oil 0.77 mg plus smaller amounts of camphor, thymol, and tolu balsam, produced significant cough reductions at the 10 through 40 minute challenge periods reaching a peak of 35 percent reduction at the 10 and 20 minute intervals whereas a control lozenge produced a significant reduction of 11 to 17 percent maximum at the 10 and 20 minute challenge periods only (Ref. 26). Similar results were obtained in 16 subjects using an active formulation containing menthol, eucalyptus oil, camphor, thymol and tolu balsum present in about one-half the amounts utilized in the preceding study (Ref. 27).

The effect of rinsing and gargling twice daily with an aqueous mixture of volatile substances on the incidence of colds and the severity of the symptoms associated with colds was evaluated in a long-term double-blind, placebo-controlled, subjective study in school children. The results of the study revealed milder nasal symptoms and cough symptoms in individuals using the medicated mouthwash as compared to the placebo. Although the medicated mouthwash contained 0.91 mg/ml eucalyptol, the results did not demonstrate the contribution of this component to the overall alleviation of symptoms (Ref. 28).

(3) *Proposed dosage.* Dosage for adults and children 2 to under 12 years is as follows: (i) For topical use as a 1.3 percent ointment preparation: To be rubbed on the throat, chest, and back as a thick layer. The area of application may be covered. However, clothing should be left loose about the throat and chest to help the vapors rise to reach the nose and mouth. Applications may be repeated up to 3 times daily.

(ii) For steam inhalation use as a 1.7 percent solution: 1 tablespoonful of solution per quart of water is added directly to the water in a hot steam vaporizer, bowl, or washbasin; or 2 teaspoonfuls of solution per pint of water are added to an open container of boiling water. Breathe in vapors during the period of medicated steam generation. May be repeated 3 times daily.

(iii) For topical use as a lozenge 0.2 to 15 mg: Allow lozenge to dissolve slowly in mouth. May be repeated every ½ to 1 hour.

(iv) For use as a mouthwash 0.91/mg/ml solution: Gargle with ⅔ oz (20 ml) twice daily.

For children under 2 years, there is no recommended dosage except under the advice and supervision of a physician.

(4) *Labeling.* The Panel recommends the Category I labeling for antitussive active ingredients. (See part III. paragraph B.1. above—Category I Labeling.) In addition, the Panel recommends the following specific labeling: (i) For topical ointment use: *Warning*: "For external use only. Do not take by mouth or place in nostrils".

(ii) For steam inhalation use: *Warning*: "For steam inhalation only. Do not take by mouth".

(5) *Evaluation.* The Panel made the following recommendations:

(i) For topical ointment use: Data to demonstrate effectiveness will be required from only one additional controlled cough-counting objective study in patients with coughs due to respiratory disease in accordance with the guidelines set forth below for testing antitussive drugs.(See part III. paragraph C. below—Data Required for Evaluation.)

(ii) For steam inhalation use: Data to demonstrate effectiveness will be required in accordance with the guidelines set forth below for testing antitussive drugs. (See part III. paragraph C. below—Data Required for Evaluation.)

(iii) For topical use as a lozenge: Data to demonstrate effectiveness will be required in accordance with the guidelines set forth below for testing antitussive drugs. (See part III. paragraph C. below—Data Required for Evaluation.)

(v) For use as a mouthwash: Data to demonstrate effectiveness will be required in accordance with the guidelines set forth below for testing antitussive drugs. (See part III. paragraph C. below—Data Required for Evaluation.)

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(28) OTC Volume 040278.

i. *Horehound (horehound fluidextract)*. The Panel concludes that horehound (marrubium) is safe but there are no data to evaluate its effectiveness for OTC use as an antitussive.

(1) *Safety*. Clinical experience has confirmed that horehound is safe in the dose ranges used as an antitussive. Horehound has been used for many centuries in the folk medicine of Europe in the form of a sweetened tea or bitter flavoring agent in decoctions and candies (Ref. 1). No adverse reactions have been cited and on the basis of long clinical experience, the Panel concludes that it is safe at the dose ranges employed for OTC use.

(2) *Effectiveness*. There are no well-controlled studies documenting the effectiveness of horehound as an antitussive. There is no information available as to the effectiveness of horehound. It is stated that it was formerly used as an expectorant in various types of bronchitis but "has been abandoned by physicians" (Ref. 2). Another text (Ref. 1) states that it was dropped from the "Primary List" of drugs in 1910.

(3) *Proposed dosage*. The Panel is unable to determine a proposed dosage.

One marketed product for children contains the following dosage range: Children over 5 years oral dosage is 44 mg. Children 2 to 5 years oral dosage is 22 mg (Ref. 3). The Panel concludes that the pharmaceutical industry should consult with the Food and Drug Administration as to a suitable dosage for testing. Otherwise, the Panel recommends that each drug manufacturer evaluate the dosage as labeled on the manufacturer's marketed product(s).

(4) *Labeling*. The Panel recommends the Category I labeling for antitussive active ingredients. (See part III. paragraph B.1. above—Category I Labeling.)

(5) *Evaluation*. Data to demonstrate effectiveness will be required according to the guidelines set forth below for testing antitussive drugs. (See part III. paragraph C. below—Data Required for Evaluation.) However, the Panel notes that if claims for antitussive activity were withdrawn, this preparation could be considered a pharmaceutical necessity or flavoring agent.

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(3) OTC Volume 040173.

j. *Menthol/peppermint Oil (topical/inhalant)*. The Panel concludes that menthol/peppermint oil is safe in the dosage ranges used when applied topically as an inhalant but there are insufficient data to permit final classification of its effectiveness for topical or inhalant OTC use as an antitussive.

(1) *Safety*. Clinical experience has confirmed that menthol/peppermint oil (topical/inhalant) is safe in the dosage ranges used as an antitussive.

Menthol is the chief constituent of peppermint oil comprising not less than 50 percent. It may be obtained by distillation of the oil or by synthesis (Ref. 1). Toxic effects with an excess ingestion of peppermint oil or mentholated products can include abdominal pain, nausea, vomiting, and symptoms of central nervous system depression such as dizziness, staggering gait, slowed respiration, flushed face, sleepiness, and coma (Refs. 2 and 3). The fatal oral dose of menthol itself in man is about 2 gm (Ref. 4). Topically applied menthol produces a cooling sensation presumably due to stimulation of the cold sensory receptors, whereas higher concentrations have irritant properties. In one study, a 20 percent solution of menthol in oil rubbed on to the skin induced an intense and lasting cooling sensation followed by numbness with slight burning and skin redness. A 0.5 percent solution applied to the nasal or oral mucosa was subjectively irritating, whereas a 0.2 percent solution was judged nonirritating (Ref. 5). A study of 223 subjects in which an ointment containing several volatile substances including menthol 2.8 percent was applied for 48 hours to areas of intact skin under a patch and to abraded skin revealed no instances of inflammation, wheal, hives, or primary irritation following the period of exposure (Ref. 6). Repeated topical application of mentholated products has been reported to give rise to hypersensitivity reactions, including contact der-

matitus (Ref. 4). A study of ten subjects who received an application of an ointment containing several volatile substances including menthol 2.8 percent to their trunks 3 times daily for 3 weeks, then 1 week off, followed by another week of treatment, revealed no local reactions during this subsequent challenge phase (Ref. 7). The incidence of hypersensitivity to menthol appears to increase with increased duration of use. For example, one survey revealed an incidence of less than 1 percent menthol hypersensitivity in 542 patients using a mentholated ointment for less than 10 years, whereas an incidence of 3.4 percent hypersensitivity was seen in 414 patients using this type of a preparation for longer than 10 years (Ref. 8).

In infants and small children under 2 years, intranasal use of ointments or drops containing high percentages of menthol may cause spasm of the glottis. A case of dangerous asphyxiation has been reported in a 3-week-old infant following intranasal application (Ref. 9). For this reason a warning against the topical application of menthol-containing products directly to the nostrils of infants has been recommended (Refs. 4 and 9). A study of infants and children with respiratory infection was made. They received an ointment containing a mixture of volatile oils including 2.8 percent menthol applied to the chest and neck; the study demonstrated no adverse effect from the inhaled vapors by that route of administration on the rate of clearing of laryngeal inflammation. In this study 35 children, 23 under 2 years of age, with respiratory infection received only standard forms of therapy, e.g., antibiotics and fluids, while 37 children, 30 under 2 years of age, received standard therapy plus the mentholated ointment to the chest and neck. Laryngoscopic examination revealed comparable rates of clearing of laryngeal inflammation (Ref. 10).

A liquid mixture of volatile substances including 3.66 percent menthol is placed in the water of a hot steam vaporizer and administered via inhalation. A number of studies involving nearly 900 subjects in which this mixture was administered at recommended doses was not associated with significant complaints of subjectively perceived adverse effects (Refs. 11 through 23). Exaggerated-use studies in adults and children, i.e., exposure for several hours to higher than recommended exposure concentrations, either due to sitting in closer proximity to the vaporizer or placing 2 to 5 times the recommended dose of the volatile substance in the vaporizer was not associated with irritating or toxic effects (Refs. 24 and 25).

In two studies, 40 healthy subjects who were each asked to dissolve two candy-base lozenges, each lozenge containing 1.36 mg of menthol together with other volatile oils, every 20 minutes for 2 hours exhibited no adverse effects with the exception of one report of nausea and vomiting. This was attributed to a dislike for the wild cherry flavor of the lozenge (Refs. 26 and 27). In a group of 70 healthy subjects, 50 adults and 20 children ages 8 to 12, half dissolved a menthol-eucalyptus lozenge containing 9.62 mg menthol and 5.55 mg eucalyptus oil every 4 to 8 hours on 2 successive days, the other half dissolved the cough drop base without the aromatics. In this intensive dosage schedule, a slightly larger number of subjects demonstrated mild irritation of the oral mucosa on days 1 and 2, but there were no differences between the two groups in the severity of irritation or residual findings after day 2. No systemic complaints were reported (Ref. 28). A similar study using a lozenge formulation containing menthol 3.14 mg and eucalyptus oil 4.625 mg versus a lozenge base without volatile substances produced comparable results (Ref. 29).

An aerosolized dosage form of volatile substances including 1 percent menthol has also been utilized for treatment of nasal congestion and cough symptoms. Rats exposed to acute overdoses of the spray in a confined chamber for 6 hours revealed no untoward behaviorial responses or airway tissues abnormality upon autopsy examination (Ref. 30). A group of four monkeys were exposed to 200 gm per day of the aerosol, i.e., 2 gm of menthol total dose in divided doses over an 8 hour period for 14 consecutive days in a confined chamber. Eye irritation was the only pharmacotoxic sign observed during the study (Ref. 31). In humans, such aerosol sprays have been generally safe when used as directed, but there have been reports of deaths from deliberate sniffing abuse, particularly when the subject inhales from a plastic bag into which the material has been sprayed (Ref. 32). Furthermore, one commercial preparation containing a particular solvent, 1,1,1-trichloroethane, was recently recalled from the market due to potential hazards of this substance (Ref. 33).

(2) *Effectiveness.* There are no well-controlled studies documenting the effectiveness of menthol/peppermint oil (topical/inhalant) as an antitussive. Its effectiveness is uncertain due to lack of properly controlled studies of the substance by itself.

The local anesthetic effect of menthol vapor has been the justification for including menthol in topically administered ointments and lozenges for alleviation of cough. In a crossover study involving 16 subjects, the effects of a 2.8 percent mentholated petrolatum ointment applied to the chest of the subjects was compared to an ointment containing several volatile substances including 2.8 percent menthol, and to petrolatum in suppressing a citric acid aerosol induced cough. A combination ointment containing menthol induced a significant decrease in cough counts at all challenge times from ½ hour through 2 hours, averaging about 20 percent decrease at the ½ and 1 hour intervals, whereas the single ingredient menthol ointment yielded a significant decrease in cough counts just at the ½ and 1 hour intervals, averaging about 10 percent reduction. The petrolatum yielded no significant decrease in cough counts compared with base line (Ref. 34). Similar results with the combination ointment containing 2.8 percent menthol were obtained in two additional induced-cough studies conducted by the same investigator (Refs. 34 and 35).

A single-blind crossover cough-counting study of 27 patients exhibiting stabilized chronic cough, utilized twice daily chest applications of either the ointment containing several volatile substances including 2.8 percent menthol, an ointment containing 1.3 percent eucalyptus oil, or petrolatum base. Neither the ointment mixture nor the eucalyptus oil ointment induced a significant decrease in cough counts compared to placebo after the morning application, but a significant 20 percent cough-count reduction compared to placebo was obtained following the afternoon dose of the ointment mixture. An average reduction in cough counts of about 10 percent compared to placebo was noted following the afternoon dose of eucalyptus oil ointment, but this was not statistically significant (Ref. 36).

A liquid mixture of volatile substances added to the water of a hot steam vaporizer and administered via inhalation contained menthol 3.66 percent, camphor 7 percent, eucalyptus oil 1.7 percent, and tincture of benzoin 5 percent. Three crossover studies compared the effects of this volatile substance containing liquid in steam, 1 tablespoonful per quart of water, to steam alone in suppressing coughs artificially induced by the citric acid aerosol technique. In each case, both steam and medicated steam induced a statistically significant reduction in cough counts during the period of administration. In two of the studies the cough reduction with the medicated steam was statistically greater than with steam alone and persisted beyond the period of actual administration to the subject (Refs. 37, 38, and 39). In an objective cough-counting study on patients with acute upper respiratory disease, the medicated steam showed significantly lower cough counts than does unmedicated steam for the 4 hours the patients were exposed to vaporization and for 2 additional hours after vaporizer therapy was discontinued (Ref. 40). Subjective evaluation studies of adults and infants having cough associated with respiratory infection demonstrated statistically significant antitussive effectiveness of the volatile substances in steam, 1 tablespoon per quart of water, and of steam alone. In some of these studies the effect of the medicated steam was judged statistically superior to the steam alone (Refs. 41 and 42).

The variety of lozenge preparations containing a mixture of volatile substances including menthol have been studied for their ability to suppress citric acid aerosol induced cough in normal subjects. Since each of these lozenge preparations contain different concentrations of menthol and other volatile substances, the results of the study will be individually summarized. The general study format involved an unblinded crossover design in which a group of

cough-standardized normal subjects were tested with each of two lozenge formulations, i.e., the active formulation and its vehicle control, against cough artificially induced by the citric acid aerosol technique. Two studies involved lozenges in which menthol was the principal active ingredient and consequently represent an indication of the effectiveness of this mode of administering menthol to suppress cough. One of the studies involving 16 subjects used a lozenge containing menthol 2.64 mg and peppermint oil 2.29 mg plus benzyl alcohol 5.76 mg. The active formulation produced significant cough reductions at the 10 to 40 minute challenge periods, reaching a peak of 30 to 35 percent at the 10 and 20 minute intervals, whereas the control lozenge produced a significant reduction of 15 to 20 percent at the 10 and 20 minute intervals only (Ref. 43). The other study of 10 subjects, utilizing a lozenge containing menthol 1.13 mg plus citric acid flavoring, produced greater cough reduction than the control lozenge at the 10 through 30 minute challenge periods, although both the active and control lozenges in this study produced cough reductions at these time intervals (Ref. 44).

Two studies involving a total of 40 subjects used similar active formulations consisting of menthol 9.6 mg and eucalyptus oil 5.5 mg per lozenge. In these studies the active formulation produced significant cough reductions at the 10 to 40 minute challenge periods, reaching a peak of 25 to 35 percent reduction at the 10 and 20 minute intervals, whereas the control lozenge produced a significant reduction of 10 to 15 percent maximum at only the 10 minute challenge (Refs. 45 and 46). In a study of nine subjects receiving lozenge doses of menthol 1.5 mg and eucalyptol 0.35 mg, elevated citric acid thresholds of 130 to 146 percent of control for 3 to 5 hours after dosing were obtained, although a placebo control lozenge was not utilized in this study for comparison (Ref. 47). Another study of 20 subjects utilizing a formulation of menthol 2.78 mg, eucalyptus oil 0.77 mg, plus smaller amounts of camphor, thymol, and tolu balsam, produced significant cough reductions at the 10 through 40 minute challenge periods, reaching a peak of 35 percent reduction at the 10 and 20 minute intervals, whereas a control lozenge produced a significant reduction of 11 to 17 percent maximum at the 10 and 20 minute challenge periods only (Ref. 48). Similar results were obtained in 16 subjects using an active formulation containing menthol, eucalyptus oil, camphor, thymol and tolu balsam present in about ½ the amounts utilized in the preceding study (Ref. 49).

The effect of rinsing and gargling twice daily with an aqueous mixture of volatile substances on the incidence of colds and the severity of the symptoms associated with colds was evaluated in a long-term, double-blind, placebo-controlled, subjective study in school children. The results of the study revealed milder nasal symptoms and cough symptoms in individuals using the medicated mouthwash as compared to the placebo. Although the medicated mouthwash contained 0.42 mg/ml menthol, the results did not demonstrate the contribution of this component to the overall alleviation of symptoms (Ref. 50).

(3) *Proposed dosage.* Dosage for adults and children 2 to under 12 years is as follows: (i) For topical use as a 2.8 percent ointment preparation: To be rubbed on the throat, chest, and back as a thick layer. The area of application may be covered. However, clothing should be left loose about the throat and chest to help the vapors rise to reach the nose and mouth. Applications may be repeated up to 3 times daily.

(ii) For steam inhalation use as a 3.66 percent solution: 1 tablespoonful of solution per quart of water is added directly to the water in a hot steam vaporizer, bowl, or washbasin; or 2 teaspoonfuls of solution per pint of water are added to an open container of boiling water. Breathe in vapors during the period of medicated steam generation. May be repeated 3 times daily.

(iii) For topical use as a lozenge 1.0 to 15 mg: Allow lozenge to dissolve slowly in mouth. May be repeated every ½ to 1 hour.

(iv) For use as a mouthwash 0.42 mg/ml solution: Gargle with ⅔ oz (20 ml) twice daily.

For children under 2 years, there is no recommended topical or inhalant dosage except under the advice and supervision of a physician.

(4) *Labeling.* The Panel recommends the Category I labeling for antitussive active ingredients. (See part III. paragraph B.1. above—Category I Labeling.) In addition, the Panel recommends the following specific labeling: (i) For topical ointment use: *Warning:* "For external use only. Do not take by mouth or place in nostrils".

(ii) For steam inhalation use: *Warning:* "For steam inhalation only. Do not take by mouth".

(5) *Evaluation.* The Panel made the following recommendations: (i) For topical ointment use: Data to demonstrate effectiveness will be required from only one additional controlled cough-counting objective study in patients with coughs due to respiratory disease in accordance with the guidelines set forth below for testing antitussive drugs. (See part III. paragraph C. below—Data Required for Evaluation.)

(ii) For steam inhalation use: Data to demonstrate effectiveness will be required in accordance with the guidelines set forth below for testing antitussive drugs. (See part III. paragraph C. below—Data Required for Evaluation.)

(iii) For topical use as a lozenge: Data to demonstrate effectiveness will be required in accordance with the guidelines set forth below for testing antitussive drugs. (See part III. paragraph C. below—Data Required for Evaluation.)

(iv) For use as a mouthwash: Data to demonstrate effectiveness will be required in accordance with the guidelines set forth below for testing antitussive drugs. (See part III. paragraph C. below—Data Required for Evaluation.)

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k. *Noscapine (noscapine hydrochloride).* The Panel concludes that noscapine is safe but there are insufficient data to determine its effectiveness for OTC use as an antitussive.

(1) *Safety.* Clinical experience has confirmed that noscapine is safe in the dosage ranges used as an antitussive. Noscapine belongs to the isoquinoline alkaloids of opium and, like papaverine, has a weak spasmolytic (relieves spasm) effect on smooth muscle but little or no effect on the heart or gastrointestinal tract (Ref. 1). There is no evidence that it causes addiction, and it is not subject to the Federal Controlled Substances Act. A large margin of safety in both animals and man has been reported (Refs. 2 and 3). Nausea, drowsiness, and lightheadedness have been reported in a few instances, but this was similar to the incidence in placebo reactors (Ref. 4). Bellville et al. (Ref. 5) found no depression of respiration with doses as high as 90 mg.

(2) *Effectiveness.* There are no well-controlled studies documenting the effectiveness of noscapine as an antitussive. Effectiveness has not been established by objective, controlled clinical trials.

For the most part, the animal studies employing a variety of methodologies for inducing cough by mechanical and chemical means have shown noscapine to have an antitussive effect equivalent to codeine (Refs. 6, 7, and 8). Controlled studies in man using experimentally induced cough have been conflicting (Refs. 4, 9, and 10). Most of the clinical trials reported have been poorly controlled subjective studies. The majority of these studies indicate that noscapine is equal to codeine in clinical effectiveness (Refs. 3 and 11 through 15).

Unlike the narcotic antitussives, respiratory depression and constipation have not been reported for noscapine. Doses as high as 90 mg have been given with no significant increase in toxicity (Ref. 16).

(3) *Proposed dosage.* Adult oral dosage is 15 to 30 mg every 4 to 6 hours not to exceed a total of 180 mg in 24 hours. Children 6 to under 12 years oral dosage is 7.5 to 15 mg every 4 to 6 hours not to exceed 90 mg in 24 hours. Children 2 to under 6 years oral dosage is 3.75 to 7.5 mg every 4 to 6 hours not to exceed 45 mg in 24 hours. For children under 2 years, there is no recommended dosage except under the advice and supervision of a physician.

(4) *Labeling.* The Panel recommends the Category I labeling for antitussive active ingredients. (See part III. paragraph B.1. above—Category I Labeling.) In addition, the Panel recommends the following specific claims referable to its central mechanism of action and its nonnarcotic designation:

(i) *Indications.* (*a*) "Calms the cough control center and relieves coughing".

(*b*) "Non-narcotic cough suppressant for the temporary control of coughs".

(*c*) "Calms cough impulses without narcotics".

(5) *Evaluation.* Data to demonstrate effectiveness will be required in accordance with the guidelines set forth below for testing antitussive drugs. (See part III. paragraph C. below—Data Required for Evaluation.) The Panel recommends that one experimentally induced cough study and one controlled study in patients with cough due to respiratory illness employing objective cough-counting techniques be performed in order to establish effectiveness as an antitussive.

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1. *Thymol (topical/inhalant)*. The Panel concludes that thymol is safe in the dosage ranges used when applied topically or as an inhalant but there are insufficient data to permit final classification of its effectiveness for topical or inhalant OTC use as an antitussive.

(1) *Safety*. Clinical experience has confirmed that thymol (topical/inhalant) is safe in the dosage ranges used as an antitussive.

Thymol is an alkyl derivative of phenol and has bactericidal, fungicidal and anthelmintic properties (Ref. 1). When hydrogenated, thymol is converted to the closely related drug, menthol (Ref. 2). The LD_{50} of thymol in mice is 1800 mg/kg orally (Ref. 3). No data were found bearing on the drug's toxicity in man. In view of thymol's relative inactivity compared to menthol, of which 50 to 120 gm "would have to be absorbed to cause poisoning" (Ref. 4), thymol is presumably relatively nontoxic.

(2) *Effectiveness*. There are no well-controlled studies documenting the effectiveness of thymol (topical/inhalant) as an antitussive. Experiments in anesthetized rabbits have indicated that thymol administered by steam inhalation augmented the concentration of soluble mucous in the respiratory tract fluid (Ref. 2). The dose administered was unknown but the concentration in the vaporizer was in excess of 81 mg/kg. The volume of secretions did not change. Much lower concentrations of menthol were effective (1 mg/kg). In man no data on effectiveness of thymol alone were found although a mixture containing thymol, menthol, eucalyptol and propylene glycol appeared to suppress citric acid induced cough (Ref. 5) and to reduce resistance in the nasal and bronchial airways (Ref. 6).

Studies involving the objective measurement of the antitussive activity of thymol were done with mixtures of volatile substances, topically applied as ointments (Refs. 7, 8 and 9), and in steam inhalations (Refs. 10 and 11). Although significant antitussive activity as compared to placebo was demonstrated, it was not evident whether the thymol component contributed to this effect.

The effect of rinsing and gargling twice daily with an aqueous mixture of volatile substances on the incidence of colds and the severity of the symptoms associated with colds was evaluated in a long-term, double-blind, placebo-controlled, subjective study in school children. The results of the study revealed milder cough symptoms in individuals using the medicated mouthwash as compared to placebo. Although the medicated mouthwash contained 0.63 mg/ml thymol the results did not demonstrate the contribution of this component to the overall alleviation of symptoms (Ref. 12).

(3) *Proposed dosage*. Dosage for adults and children 2 to under 12 years is as follows: (i) For topical use as a 0.1 percent preparation: To be rubbed on the throat, chest, and back as a thick layer. The area of application may be covered. However, clothing should be left loose about the throat and chest to help the vapors rise to reach the nose and mouth. Applications may be repeated up to 3 times daily.

(ii) For inhalation use as a 0.13 percent solution: 1 tablespoonful of solution per quart of water is added directly to the water in a hot steam vaporizer, bowl or washbasin; or 2 teaspoonfuls of solution per pint of water are added to an open container of boiling water. Breathe in vapors during the period of medicated steam generation. May be repeated 3 times daily.

(iii) For inhalation use as a 0.1 percent room spray: Spray room for 15 to 20 seconds in the vicinity of the patient. May be repeated at ½ to 1 hour intervals as needed.

(iv) For topical use as a lozenge 0.2 to 15 mg: Allow lozenge to dissolve slowly in mouth. May be repeated every ½ to 1 hour.

(v) For use as a mouthwash 0.63 mg/ml solution: Gargle with ⅔ oz (20 ml) twice daily.

For children under 2 years, there is no recommended dosage except under the advice and supervision of a physician.

(4) *Labeling*. The Panel recommends the Category I labeling for antitussive active ingredients. (See part III. paragraph B.1. above—Category I Labeling.) In addition, the Panel recommends the following specific labeling: (i) For topical ointment use: *Warning:* "For external use only. Do not take by mouth or place in nostrils".

(ii) For steam inhalation use: *Warning:* "For steam inhalation only. Do not take by mouth".

(5) *Evaluation*. The Panel made the following recommendations: (i) For topical use: Data to demonstrate effectiveness will be required in accordance with the guidelines set forth below for testing antitussive drugs. (See part III. paragraph C. below—Data Required for Evaluation.)

(ii) For inhalation use: Data to demonstrate effectiveness will be required in accordance with the guidelines set forth below for testing antitussive drugs. (See part III. paragraph C. below—Data Required for Evaluation.)

(iii) For inhalation use as a room spray: Data to demonstrate effectiveness will be required in accordance with the guidelines set forth below for testing antitussive drugs. (See part III. paragraph C. below—Data Required for Evaluation.)

(iv) For topical use as a lozenge: Data to demonstrate effectiveness will be required in accordance with the guidelines set forth below for testing antitussive drugs. (See part III. paragraph C. below—Data Required for Evaluation.)

(v) For use as a mouthwash: Data to demonstrate effectiveness will be required in accordance with the guidelines set forth below for testing antitussive drugs. (See part III. paragraph C. below—Data Required for Evaluation.)

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m. *Turpentine oil (spirits of turpentine) (topical/inhalant)*. The Panel concludes that turpentine oil is safe in the dosage ranges used when applied topically or as an inhalant but there are insufficient data to permit final classification of its effectiveness for topical or inhalant OTC use as an antitussive.

(1) *Safety.* Clinical experience has confirmed that turpentine oil is safe when applied topically or used as an inhalant in the dosage ranges used as an antitussive. The Panel concludes that oil of turpentine is safe when applied externally or vaporized in boiling water as a steam inhalant. However, the Panel has determined elsewhere in this document that it is not safe for OTC use when used orally as an antitussive. (See part III. paragraph B.2.b. above—Turpentine oil (spirits of turpentine) (oral).)

Oil of turpentine is a volatile oil consisting of a mixture of pinenes derived from the oleoresin obtained from Pinus palustrus. Nelson et al. (Ref. 1) found exposure to a vapor of 420 to 560 mcg/l acceptable to most of their human subjects. The threshold for industrial exposure for 8 hours has been set at 560 mcg/l. The maximum concentration obtainable with a currently marketed OTC preparation is 36 mcg/l (Refs. 2 and 3). No histological evidence of pulmonary lesions were seen in mice and rats exposed to lethal concentrations of turpentine vapors (Ref. 4). Inhalation of 300 mcg/l of turpentine vapor by mice for 15 minutes did not influence the electrocardiogram, respiratory minute volume, pulmonary airway, resistance, or compliance (Ref. 5). One study in mice using a mixture of volatile oils, one of which was turpentine, showed a decrease in pulmonary antibacterial activity (Ref. 6). Two other studies showed no change when the mixture was used (Refs. 7 and 8).

In several studies in children and infants suffering from minor breathing discomforts associated with the "common cold" no side effects that were drug related were observed when a medicated steam was administered (Refs. 9 through 13). Turpentine has been widely used as a part of a mixture of volatile oils for many years with approximately two complaints per million packages purchased (Ref. 14).

(2) *Effectiveness.* There are no well-controlled studies documenting the effectiveness of turpentine oil (topical/inhalant) as an antitussive. Its effectiveness is uncertain due to a lack of properly controlled studies of the substance by itself.

(3) *Proposed dosage.* Dosage for adults and children 2 to under 12 years is as follows: (i) For topical use as a 4.0 percent ointment preparation: To be rubbed on the throat, chest, and back as a thick layer. The area of application may be covered. However, clothing should be left loose about the throat and chest to help the vapor rise to reach the nose and mouth. Applications may be repeated up to 3 times daily.

(ii) For steam inhalation use as a 5.5 percent solution: 1 tablespoonful of solution per quart of water is added directly to the water in a hot steam vaporizer, bowl, or washbasin; or 2 teaspoonfuls of solution per pint of water are added to an open container of boiling water. Breathe in vapors during the period of medicated steam generation. May be repeated 3 times daily.

For children under 2 years, there is no recommended topical or inhalant dosage except under the advice and supervision of a physician.

(4) *Labeling.* The Panel recommends the Category I labeling for antitussive active ingredients. (See part III. paragraph B.1. above—Category I Labeling.) In addition, the Panel recommends the following specific labeling: (i) For topical ointment use: *Warning:* "For external use only. Do not take by mouth or place in nostrils".

(ii) For steam inhalation use: *Warning:* "For steam inhalation only. Do not take by mouth".

(5) *Evaluation.* The Panel made the following recommendations:

(i) For topical ointment use: Data to demonstrate effectiveness will be required from only one additional well-controlled cough-counting objective study in patients with coughs due to respiratory disease in accordance with the guidelines set forth below for testing antitussive drugs. (See part III. paragraph C. below—Data Required for Evaluation.)

(ii) For steam inhalation use: Data to demonstrate effectiveness will be required in accordance with the guidelines set forth below for testing antitussive drugs. (See part III. paragraph C. below—Data Required for Evaluation.)

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Category III Labeling

The Panel concludes that the available data are insufficient to permit final classification of the labeling claims identified below for antitussives. The Panel concludes that certain words used in the context of claims for antitussives are statements which have no scientific meaning and therefore are misleading to the consumer. Additional data are required to support the following antitussive claims:

a. The term "soothing" in labeling such as "Calms coughing by soothing the irritated throat".

b. The term "throat soothing" in labeling such as "Throat soothing and recommended for coughs due to colds and dry, husky or tickling throats".

c. The term "smooth coating" in labeling such as "Produces a smooth coating that gives quick comfort to irritated throats and helps relieve coughs".

d. The terms "demulcent action" and "soothes" in labeling such as "Demulcent action which gently sooths cough-irritated throat membranes".

e. Statements referring to "duration of action" unless there is acceptable documentation to verify this.

f. Terms relating to sleep such as "Quiets annoying cough and lets you sleep". An antitussive is capable of quieting annoying cough, but has not been demonstrated to be directly related to sleep.

g. The term "soothing" has not been scientifically demonstrated to have an antitussive effect. In fact, none of the antitussive ingredients reviewed by the Panel have any "soothing" properties since the Panel cannot determine what such a property would be. The same is true for the term "smooth". Again, the Panel is unaware of how the ingredients act to smooth an irritated throat or sooth membranes by a "demulcent" action.

C. DATA REQUIRED FOR EVALUATION

The Panel has agreed that the protocols recommended in this document for the studies required to bring a Category III drug into Category I are in keeping with the present state of the art and do not preclude the use of any advances or improved methodology in the future.

1. *Principles in the design of an experimental protocol for testing antitussive drugs.* a. *General principles.* The effectiveness of an antitussive agent is dependent on its ability to relieve the coughing of patients with a variety of disease conditions associated with cough. Relief of coughing may occur with a reduction in the frequency or number of coughs, or with a decrease in the intensity of the coughing, or both. Because coughing is such a common symptom occurring in health as well as disease, adaptation readily occurs to the extent that many patients are unaware of the extent of their coughing, and hence any subjective evaluation is apt to be highly variable and with an unacceptable margin for error. Objective studies employing the actual recording of the cough are re-

quired to document a decrease in cough frequency and/or intensity.

b. *Selection of patients.* The study design will depend on whether the patients in the study have chronic lung disease or acute self-limiting illnesses. For a cough study in patients with chronic lung disease, a crossover design could be used in a small group of 10 to 20 patients whose underlying chronic pulmonary disease is relatively stable so that daily fluctuations in the recorded cough counts performed prior to drug administration are minimized. The smoking habit of the patients must be carefully documented and maintained at the same level throughout the clinical trials. No smoking would be permitted during the actual recording sessions. For a cough study in patients with acute upper respiratory infection, a larger number of patients, averaging between 50 and 100, would have to be studied because of the marked variation in cough from day to day and hour to hour in upper respiratory infection. The patients would have to be assigned in a randomized design to either the placebo or drug groups. The sensitivity of this type of study could be improved by matching the groups for age, sex, severity of cough, and smoking habit.

c. *Methods of study.* To establish effectiveness of a drug as an antitussive, objective controlled studies employing cough-counting techniques are recommended. Two types of investigation are acceptable to the Panel. These are:

(1) A study may be done in a small group of healthy volunteers, approximately 10 to 20 in number, who are preferably nonsmokers. If smokers are included, their smoking habits must be well documented and remain at the same level during the entire course of the study. Any departure from smoking habits must be documented and made part of the evaluation of data. The data obtained in such a study including smokers and nonsmokers should be evaluated separately before combined. A challenge technique employing an irritant aerosol such as citric acid is used to assess effectiveness, dose, and time responses against the experimentally induced cough. This is performed under controlled laboratory conditions with a double-blind or suitably blinded, crossover design in suitably trained individuals.

(2) A double-blind, controlled study may be done in patients with cough due to respiratory disease. The dose and formulation of the drug to be tested would be as recommended for OTC use. Coughs are recorded and counted for stated periods before and after giving the drug or placebo so that adequate comparisons can be made concerning the onset and duration of antitussive activity following a single dose, as well as the effect of multiple doses. As a model for OTC drugs, however, the requirement for long periods of testing would be unnecessary since effective relief should be obtained fairly rapidly and, in most instances, after 1 or, at most, 2 days.

d. *Interpretation of data.* Evidence of drug effectiveness is required from a minimum of two positive studies based on the results of two different investigators or laboratories. All of the required studies in man should employ objective cough-counting techniques for recording the cough reflex. In the reevaluation of those drugs for which there was insufficient evidence of antitussive effectiveness and for the assessment of drugs that have not been submitted for review by the Panel, the two required studies should consist of either one challenge study with experimentally induced cough plus a study with cough in respiratory disease, or, alternatively, two studies by different investigators in patients with respiratory disease. A significant reduction in cough when compared with placebo by acceptable statistical analysis of the data will permit reclassification of such drugs into Category I.

All data submitted to the Food and Drug Administration must present both favorable and unfavorable results.

e. *Evaluation of safety.* Tests for safety should involve the usual tests for toxicity relevant to the known possible adverse effects of the drugs under testing. Tests should be done in the form of dose-response curves up to maximum therapeutic effectiveness.

IV. EXPECTORANTS

A. GENERAL DISCUSSION

Expectorants are agents that are used to promote or facilitate the evacuation of secretions from the bronchial airways to provide for the temporary relief of coughs due to minor throat and bronchial irritation as may occur with upper respiratory infection. This may be accomplished by reducing the thickness of these secretions or by augmenting the formation of a more fluid secretion. The secretions (sputum or phlegm) expectorated consists in part of respiratory tract fluids (RTF) together with a varying mixture of saliva and postnasal secretions.

In general, the mechanisms of action of the expectorants have been shown to be due to one or more of the following: The stimulation of reflexes from the stomach (the major action of certain drugs that are irritants to the gastrointestinal tract and act through their nauseant effect which increases the output from the secretory glands of the gastrointestinal as well as the respiratory tracts); stimulation of vagal nerve endings in the glands of the bronchial tubes; direct effect on the secretory cells lining the airway when administered by inhalation or if excreted by the respiratory tract; and stimulation of centers in the brain such as the vomiting center.

By facilitating the evacuation of secretions from the bronchial airway, local irritants are removed. In addition, by increasing the amount of mucous that covers and protects the lining of the throat and the bronchial airway, it is claimed that a "soothing" or demulcent" action is exerted which relieves irritated membranes in the respiratory passages. While these effects may indirectly serve to diminish the tendency to cough, the mechanism of this indirect action is quite different from that of an antitussive which is specifically designed to inhibit or suppress cough. Any claim relating to the amelioration of cough must be supported by the type of studies suggested above for evaluation of antitussives. (See part III. paragraph C. above—Data Required for Evaluation.) Expectorants would be expected to have their major usefulness in the irritative nonproductive cough as well as those coughs productive of scanty amounts of thick, sticky secretions.

As a group, the expectorant drugs have been widely used for many decades in the form of liquid preparations. By and large, in the dosages used for OTC administration, these drugs have had a good safety record. The few exceptions, where hypersensitivity reactions or cumulative toxicity represents a distinct hazard, have been discussed under the individual sections. While the expectorants have been traditionally used for their effect on aiding in the expectoration of phlegm (sputum) and thus relieving certain aspects of difficulty in breathing, there is little or no evidence to document this. In summary, the Panel concludes that while many of the expectorants on the market with long usage are generally safe, most lack evidence of efficacy and furthermore, all expectorants must be clearly identified on the labels of drug products as having a primary effect on respiratory sputum and not primarily as an antitussive.

B. CATEGORIZATION OF DATA

1. *Category I conditions under which expectorant ingredients are generally recognized as safe and effective and are not misbranded.*

Category I Active Ingredient

The panel was unable to classify a claimed expectorant active ingredient as generally recognized as safe and effective and not misbranded.

Category I Labeling

The Panel recommends the following Category I labeling for expectorant active ingredients to be generally recognized as safe and effective and not misbranded:

a. *Indications.* (1) "Helps loosen phlegm (sputum)".

(2) "Helps rid the passageways of bothersome mucus".

(3) "Expectorant action to help loosen phlegm (sputum) and bronchial secretions".

(4) "Helps drainage of the bronchial tubes by thinning the mucus".

(5) "Relieves irritated membranes in the respiratory passageways by preventing dryness through increased mucus flow".

b. *Warnings.* (1) "Do not give this product to children under 2 years except under the advice and supervision of a physician".

(2) "Do not take this product for persistent or chronic cough such as occurs with smoking, asthma, or emphysema, or where cough is accompanied by excessive secretions except under the advice and supervision of a physician".

(3) *"Caution:* A persistent cough may be a sign of a serious condition. If cough

persists for more than 1 week, tends to recur or is accompanied by high fever, rash or persistent headache, consult a physician".

2. *Category II conditions under which expectorant ingredients are not generally recognized as safe and effective or are misbranded.* The use of expectorants under the following conditions is unsupported by scientific data, and in some instances by sound theoretical reasoning. The Panel concludes that the following ingredients and labeling should be removed from the market until scientific testing supports their use.

Category II Active Ingredients

The Panel has classified the following expectorant active ingredients as not generally recognized as safe and effective or as misbranded:

Antimony potassium tartrate
Chloroform
Iodides: Calcium iodide anhydrous, Hydriodic acid syrup, Iodized lime, Potassium iodide
Ipecac fluidextract
Squill preparations: Squill, Squill extract
Turpentine oil (spirits of turpentine) (oral)

a. *Antimony potassium tartrate.* The Panel concludes that antimony potassium tartrate is not safe for OTC use as an expectorant.

(1) *Safety.* Antimony potassium tartrate is not safe in the dosage range used as an expectorant.

The trivalent salts of antimony are potent inducers of vomiting; they act on centers in the brain as well as locally on the stomach walls. Because the antimony ingredient in this preparation tends to accumulate in the body and not to be excreted in a manner similar to arsenic, the danger of toxic reactions increases with repetitive or chronic use. These toxic reactions consist of marked irritation of the stomach and intestinal mucosa. Pain in joints and muscles are common, and the muscles of the heart may be depressed. Abdominal pain, rash and vascular collapse as well as a number of cases of hemolytic anemia, some fatal, have been reported (Ref. 1). Such toxic effects have been seen with the use of the trivalent compound at higher doses for the treatment of helminthic infections; but even in doses suitable for expectorant activity, antimony potassium tartrate is considered too toxic because of its cumulative properties to be used as an OTC product (Ref. 1).

(2) *Effectiveness.* There is no evidence that antimony potassium tartrate is effective as an expectorant.

When administered in subemetic doses, antimony potassium tartrate theoretically exerts its expectorant activity through reflex stimulation of the salivary and bronchial glands (Ref. 2). There is, however, not one documented study in either animals or man demonstrating its effect on cough, sputum production or respiratory tract secretions (Ref. 3).

(3) *Evaluation.* Because of its toxicity and tendency to accumulate in the body, the Panel is of the opinion that even subemetic doses present risks which outweigh whatever benefit theoretically might occur since there is no evidence to support effectiveness.

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b. *Chloroform.* The Panel concludes that chloroform is not effective for OTC use as an expectorant. The Panel is aware that the safety of chloroform is being questioned at present and has therefore limited its use only as a flavoring agent in CCABA preparations.

(1) *Safety.* The Panel concludes that the question of safety is dependent on dosage and abuse potential.

In doses of 4 to 8 ml orally, chloroform has been known to produce a narcotism similar to that occurring when administered by inhalation but developing more slowly and of longer duration (Ref. 1). The mean lethal dose by ingestion is approximately 30 ml (Ref. 2), although as little as a teaspoonful has produced serious illness. Symptoms of toxicity due to chloroform ingestion are often delayed for 2 or more days (Ref. 3). The problem of abuse at a "chloroform party" has recently been reported (Ref. 4).

Three documents concerning the safety of chloroform were submitted to the Panel for review and appropriate action. These pertained to the possible carcinogenicity of chloroform (Refs. 5 and 6) and the acute toxicity of chloroform in rats with an extrapolation to a suggested "maximum permissible limit" in humans (Ref. 7).

The first document was a review of a report by Harris on the implications of cancer causing substances in Mississippi River water (Ref. 5). A detailed analysis of the epidemiological data, presented together with a review of the statistical methods and the animal studies, is reported in full in the minutes of the 17th meeting of the Panel, Appendix 9 (Ref. 8). The Panel recognizes that there are serious inconsistencies in the report which makes the extrapolation of the data to possible risks of cancer from chloroform in drinking water unacceptable. Furthermore, the evidence of carcinogenicity in mice is conflicting and inconclusive and its extrapolation to another species, man, is open to serious question. Accordingly, the Panel concludes that for the report pertaining to the possibility of chloroform being a carcinogen in drinking water there is no evidence to support this possible carcinogenic hazard in the recommended dosages. This view is supported by an ad hoc Study Group on "Assessment of Health Risk from Organics in Drinking Water" in their report to the Hazardous Materials Advisory Committee of the Environmental Protection Agency (Ref. 9).

The second document (Ref. 7) attempts to establish some guidelines on permissible limits of solvent residues in chemicals. The authors list the obvious limitations of their study, i.e., the difficulty of extrapolating from rat to man; an acute single dose study does not provide an answer regarding the effect of chronic exposure; and the questionable use of arbitrary conversion factors that have no scientific basis. Their revised figure for the permissible limit for chloroform is 0.25 ml/60 kg. The Panel's recommended concentration of 0.4 percent by volume is therefore well within the authors' suggested permissible limit. The Panel recommends that chloroform be available only as a flavoring agent at a maximum concentration of 0.4 percent which represents 0.004 ml/ml or 0.02 ml/5 ml (teaspoon) of a product dosage. This is well within their revised permissible limit of 0.25 ml/60 kg. of body weight.

The third document is a preliminary report from the National Cancer Institute entitled, "Report on Carcinogenesis Bioassay of Chloroform" dated February 1976 (Ref. 6). The protocol consisted of a total of 400 rats and mice with suitable control animals receiving daily doses of chloroform orally for a total of 546 days. The treated animals were divided into low and high dose groups.

For rats, the results of the study showed a decreased survival rate which appeared dose related. Clinical evidence of toxicity appeared during the first 10 weeks but became more apparent during the second year of the study. The control groups also showed these signs by the 70th week. Transient palpable nodules were noted in both test and control groups by the end of the second year. The incidence of "all tumors" in both treated and control rats did not differ. Significant differences from control groups occurred with kidney tumors in male rats which appeared dose related and thyroid tumors in the female rats but the thyroid tumors were not considered relevant to the study because of the known incidence of spontaneously occuring thyroid tumors in this strain of rat. Neoplastic nodules of the liver occurred with equal frequency in test and matched controls (5 percent). Necrosis of hepatic parenchyma occurred with slightly greater frequency in the chloroform-treated rats.

For mice, results of the study showed that there were no significant differences in survival rate between the controls and treated mice except for the high dose female group. Beginning after 42 weeks of treatment, the chloroform-treated mice began to exhibit a bloated appearance with abdominal distention. The incidence of "all tumors" in the treated groups was significantly higher, and this was solely due to the presence of hepatocellular cancer.

The conclusions to be drawn from this study are that orally administered chloroform can produce hepatic neoplasms in this strain of mice when administered at these levels and for a prolonged period of time. There was a less striking correlation of kidney tumors with chloroform ingestion in the rat species. But the lack of any increase in hepatic tumors in the rats or kidney tumors

in the mice is attributed by the authors as illustrating "species differences in organ specificity and sensitivity." The Panel questions whether this then can be extrapolated to other species such as dog or man.

The Panel has considered the dosage of chloroform administered in the study. The average 400-gm rat received 36 to 80 mg/day for 546 days or a total of 19.-656 to 43.680 gm. The average 30-gm mouse received 4 to 14 mg/day for 546 days or a total of 2.184 to 7.644 gm. In terms of an average 60-kg human, the equivalent doses would be 5.4 to 12.0 gm/day or a total of 2,984.4 to 6,552 gm for 546 days. If the mouse dosage is extrapolated, the human dose would be 8.0 to 28.0 gm/day or a total of 4,368 to 15,288 gm. The Panel finds that the use of chloroform as a flavoring agent at a maximum allowable concentration of 0.4 percent or 0.4 gm/100 ml would require the consumption of 1.35 to 7 liters/day for a total of 737.1 to 8,822 liters in 546 days. If the usual cough mixture is dispensed in a 120 ml bottle, this would represent the consumption of 31,850 bottles in a 2-year period. The Panel questions how many other drugs, food stuffs, flavoring agents, etc. would be toxic or even carcinogenic at these levels.

In the final analysis, the Panel is unable to determine from the available data the lack of safety of chloroform in man at the 0.4 percent concentration proposed for use as a flavoring agent. Obviously, there is a dose-response relationship with respect to toxicity and the potential for abuse exists just as with alcohol.

(2) *Effectiveness.* There is no evidence that chloroform is effective as an expectorant or that it ameliorates cough.

There is no documentation of the expectorant activity of chloroform. One report (Ref. 9) states that it is "probably harmless as well as useless in the dosages used." *The U.S. Dispensatory* reports that chloroform has been added to cough mixtures as a respiratory sedative, but its action is too fleeting to be of any great value (Ref. 1). *Remington's Practice of Pharmacy* (Ref. 10) classifies chloroform as a pharmaceutical necessity.

(3) *Evaluation.* The Panel concludes that chloroform should be restricted to use as a flavoring agent (pharmaceutical necessity) in amounts not to exceed 0.4 percent by volume in an OTC CCABA product.

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c. *Iodides (calcium iodide anhydrous, hydriodic acid syrup, iodized lime, potassium iodide).* The Panel concludes that the iodides are neither safe nor effective for OTC use as expectorants.

(1) *Safety.* At a dosage that may be effective, iodides are not considered safe as OTC preparations.

The action and toxic effects of these compounds are due to the iodide content. The iodides are readily absorbed from the gastrointestinal tract and concentrated primarily in the secretions of the respiratory tract. The Panel is unaware of any animal studies on the safety of the iodides. There are no controlled studies on short-term use of iodides as expectorants. The incidence of side effects and toxicities are directly proportional to the dose and duration of therapy, and practically all persons continually treated with high doses will manifest symptoms of iodism which may simulate the symptoms of the "common cold". Some individuals, though not frequently, are highly sensitive to iodides and will react to the first few doses with serious consequences (Ref. 1). The clinical experience with iodides has been mostly in the treatment of chronic diseases, such as bronchial asthma, chronic bronchitis, bronchiectasis and emphysema; therefore, most of the toxicity has been related to chronic administration. The effective dose is 900 mg daily in divided doses (Refs. 2 and 3). Leonardy (Ref. 4) estimates the optimal dose at 25 to 35 mg/kg daily in divided doses. At these doses, there is a high incidence of toxic effects varying in seriousness from mild iodism to generalized papulovesicular eruptions, hypothyroidism, edema of the glottis, submandibular adenitis (Ref. 1), and iodide fever (Ref. 5).

Murray and Stewart (Ref. 6) reported two cases of iodide goiter and found at least 170 cases in the literature as well as several other cases through personal communications. Carswell, Kerr and Hutchison (Ref. 7) reported iodide-induced goiters in the fetuses of pregnant women. Two cases of neonatal death apparently due to congenital goiter caused by iodides compressing the trachea are reported by Galina, Avnet and Einhorn (Ref. 8). Continued heavy use in children and adults may produce goiter and/or hypothyroidism (Refs. 9 and 10). *The Medical Letter* (Ref. 11) discusses the hazards of drug-induced goiters and cites iodides as the most frequent cause. The blood levels needed to induce goiter could not be established. Falliers et al. (Ref. 2), in a double-blind crossover study of 52 asthmatic children, found a high incidence of adverse effects. One child could not complete the study because of the development of a severe generalized papulovesicular eruption. Sixteen adolescents developed acne-form lesions. Eighteen showed thyroid enlargement but no evidence of suppressed thyroid functions. Leonardy (Ref. 4), in discussing the use of iodides in the treatment of bronchial asthma, cites a review by Peacock and Davison (Ref. 12) of 500 cases in which 13.5 percent of patients receiving iodides had sufficient side effects to warrant discontinuing the drug.

There is a wide variety of diseases which contraindicate the use of iodides or require caution that the consumer does not have the expertise to determine, such as hypersensitivity to iodides, thyroid disease, psoriasis (Refs. 3 and 13) and various types of dermatoses.

Because of the high incidence of untoward effects and the potential for toxicity, iodides should be used only under the advice and supervision of a physician.

(2) *Effectiveness.* Iodides may be effective as an expectorant when given in adequate doses in some chronic respiratory disease. There is no evidence that they are efficacious in acute upper respiratory infections.

Animal studies have demonstrated the presence of iodides in the respiratory tract fluid (RTF) and an increase in the amount of RTF or a decrease in its viscosity (Refs. 14 and 15). Numerous investigators have reported observations on the expectorant action of iodides (Ref. 14). Many cite the rapid appearance of iodides in the RTF after the administration (Refs. 16, 17, and 18). The mechanism of the action of iodides as expectorants is not clear. Their presence in the RTF does not necessarily indicate increased amounts of RTF or decreased viscosity. It has been suggested by Lieberman and Kurnick (Ref. 19) that the iodides may liquefy purulent sputum by inducing the enzymatic hydrolysis of proteins. In asthmatics, no consistent change in viscosity resulting from iodides was reported by Leonardy (Ref. 4), citing as evidence a number of studies. Hirsh et al. (Ref. 20), using a new technique to measure viscosity, have been able to obtain consistent and reproducible results, but no final answer is yet available.

Falliers et al. (Ref. 2), in a 3-year double-blind study of 52 children with chronic asthma, demonstrated a statistically significant improvement in the children receiving potassium iodide 300 mg 3 times daily. The population receiving iodides improved but there was a wide variability in the response of the individuals in the study, and there is no an-

swer to why. It may be due to some other property than that of its expectorant property.

While the iodides are possibly expectorants, there are insufficient studies to confirm this. This would suggest the need for more controlled studies and better techniques for evaluation of the action of iodides.

(3) *Evaluation.* The Panel concludes that iodides are not safe for OTC use. Because of the wide variety of diseases which contraindicate their use and because of the potential for toxicity and untoward effects, iodides should be used only under the advice and supervision of a physician.

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d. *Ipecac fluidextract.* The Panel concludes that ipecac fluidextract is not safe for OTC use as an expectorant.

(1) *Safety.* Based on its long history of use, it is generally accepted that syrup of ipecac is safe although no studies can be found to substantiate this belief (Ref. 1). The fluidextract of ipecac, however, is 14 times more potent than the syrup (Ref. 2) possessing a 2 percent total alkaloidal content. The chief alkaloids of ipecac are emetine and cephaeline varying in ratio from equal parts to a fourfold preponderance of emetine. These alkaloids are responsible for its therapeutic and toxic manifestations (Ref. 3).

Toxic, even fatal doses may occur in man at 2 oz of the fluidextract. A dose of 10 ml produced death in a 4-year-old child (Ref. 4). Death from the ingestion of the syrup has not been reported. However, it is believed that many cases of overdosage result from mistaking the fluidextract for the syrup. Toxic manifestations of overdosage include nausea, bloody stools, and vomitus, cramping, and abdominal pain. Myocardial manifestations have also been reported (Ref. 3).

The Panel is aware of a reference to an expectorant dose of the fluidextract of 0.2 to 0.5 ml (Ref. 5), however the Panel feels that the syrup possesses a superior benefit-to-risk ratio and that ipecac fluidextract should not be available for OTC use as an expectorant.

(2) *Effectiveness.* Ipecac fluidextract has both local and central effects; however, there are no acceptable clinical studies to substantiate its use as an expectorant.

(3) *Evaluation.* The Panel is unable to determine a safe dose for ipecac fluid extract for use as an expectorant. Because of its documented toxicity and since there is no evidence to support effectiveness, the Panel concludes that ipecac fluidextract is not safe for use as an expectorant.

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e. *Squill preparations (squill, squill extract).* The Panel concludes that squill preparations are not safe or effective for OTC use as expectorants.

(1) *Safety.* Squill is a toxic substance capable of causing nausea, vomiting, and violent purging. It contains scillarin A and scillarin B, glycosides that may be toxic to the heart. The powdered drug and extracts from it have been used as rat poison. As a rat poison, red squill is usually preferred but all squill preparations have the same general properties (Ref. 1). Although the market experience would indicate that squill is probably safe, the doses used are small and there are no data available to relate this dose to effectiveness or to the lower limits of toxic doses (Ref. 2). Available information relates to sources and methods for preparation. The lowest toxic dose is currently estimated at 50 mg/kg (Ref. 3).

(2) *Effectiveness.* Squill is an irritant to the gastric mucosa and produces a reflex expectorant action. In larger doses it is an emetic (Refs. 1, 4, and 5). There are no available data to relate these effects to dose. Squill is practically always given as one of several drugs in various preparations and there are no data to indicate whether it does or does not contribute to the expectorant action of the preparation.

(3) *Evaluation.* Because of its known toxicity and historical use as a rat poison, and since there are no data available to relate marketed doses as an expectorant to the lower limits of toxic doses, the Panel is of the opinion that the risks outweigh whatever benefit might occur. Therefore, the Panel concludes that squill preparations are not safe or effective for OTC use.

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f. *Turpentine oil (spirits of turpentine) (oral).* The Panel concludes that oil of turpentine is not safe for OTC use when taken orally as an expectorant.

(1) *Safety.* Oil of turpentine is a volatile oil distilled from turpentine, an oleoresin obtained from the pine tree. It has a characteristic odor and taste. The substance has been administered orally, topically and by inhalation.

In doses of 15 ml in children and 150 ml in adults fatal poisoning may occur (Ref. 1). Excessive oral doses produce marked irritation of the alimentary tract, especially of the stomach and of the pelvic organs. Toxic symptoms include vomiting, diarrhea, acute pain,

renal irritation, bloody stools and hyperemia of all abdominal organs. Continued oral use may lead to cloudy swelling and fatty degeneration of the liver. Abnormal central nervous system symptoms may develop (Refs. 2 and 3).

Since no safe oral dose has been established for effective use as an expectorant, the Panel concludes that turpentine oil should not be available for oral OTC use as an expectorant. However, elsewhere in this document, the Panel concludes that the ingredient is safe when applied topically or used as an inhalant but that there are insufficient data to permit final classification of its effectiveness for inhalant or topical use as an expectorant. (See part IV. paragraph B.3.n. below—Turpentine oil (spirits of turpentine) (topical/inhalant).)

(2) *Effectiveness.* Oil of turpentine is irritating and its chief suggested uses are based on this property (Refs. 1 and 4). There is no evidence to support its effectiveness as an expectorant when taken orally.

(3) *Evaluation.* The Panel is unable to determine a safe oral dose for turpentine oil for use as an expectorant. The Panel is of the opinion that the risk from oral administration outweighs whatever benefit might occur. Therefore, the Panel concludes that turpentine oil is not safe for oral use as an expectorant.

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Category II Labeling

The Panel concludes that the use of certain labeling claims related to the safety and/or effectiveness of the product are unsupported by scientific data, and in some instances by sound theoretical reasoning. The Panel has previously discussed such labeling. (See part II. paragraph O. above—CCABA Product Labeling Claims Not Supported by Scientific Evidence.) However, labeling that is descriptive of the product such as its taste or appearance are acceptable.

The Panel concludes that the following claims are misleading and are unacceptable for preparations used as expectorants. These and similar claims are unsupported by scientific data. The term "congestion", which may be interpreted by the target population to denote a discomfort of the chest, may result from a variety of causes, several of which may be of a most serious nature and require professional attention. Other terms and phrases are descriptive, but vague, and cannot be scientifically evaluated. Statements or phrases which allude to greater potency or suggest superiority of a product are not acceptable.

All claims that state or imply a therapeutic action or safety property peculiar to the preparation that cannot be demonstrated in controlled studies are not acceptable, e.g., "specially formulated", "improved", "selected", "natural", "extra strength", "teamed components", "superior to ordinary", "modern", and "superior".

Claims implying a physiological effect that has no foundation or meaning or will be meaningless to the public are unacceptable; such as "antiallergic", "gets at the roots of", "fights", "wakes up", "recommended by doctors", "multiaction", and "travels through the blood stream", "works internally", and "actively moistens".

Claims for relief where time is indeterminate and not supported by scientific data are unacceptable, such as "fast" and "prompt". Using the above criteria the Panel feels that the following specific claims are unacceptable:

a. *Unacceptable claims because of vagueness and the inability to evaluate them scientifically.* (1) "Temporarily relieves cough congestion by working internally to break up phlegm".

(2) "Help decongest bronchial passage".

(3) "To help clear congestion".

(4) "Frees secretions along lower respiratory tract".

(5) "Helps loosen congestion so you can cough it up and get it off your chest".

(6) "Works internally".

(7) "Actively moistens the bronchial lining".

(8) "Soothes tired throats".

(9) "Promotes free breathing".

(10) "Restores free breathing".

(11) "Eases breathing".

b. *Unacceptable because the claims allude to greater potency or suggest superiority of a product which is not supported by scientific data.* (1) "Full expectorant".

(2) "Combines modern expectorant".

(3) "Superior expectorant".

3. *Category III conditions for which the available data are insufficient to permit final classification at this time.* The Panel concludes adequate and reliable scientific evidence is not available at this time to permit final classification of the claimed conditions listed below. Because of the lack of suitable objective criteria for evaluating expectorant activity and the need to rely on subjective assessment of highly variable symptoms, the Panel believes it reasonable to provide 5 years for the development and review of such evidence. Marketing need not cease during this time if adequate testing is undertaken. If adequate effectiveness data are not obtained within 5 years, however, the conditions listed in this category should no longer be marketed as over-the-counter products.

Category III Active Ingredients

The Panel has concluded that the available data are insufficient to permit final classification of the following claimed expectorant active ingredients:

Ammonium chloride
Beechwood creosote
Benzoin preparations (inhalant): Compound tincture of benzoin, Tincture of benzoin
Camphor (topical/inhalant)
Eucalyptol/eucalyptus oil (topical/inhalant)
Glyceryl guaiacolate
Ipecac syrup
Menthol/peppermint oil (topical/inhalant)
Pine tar preparations: Extract white pine compound, Pine tar, Syrup of pine tar, Compound white pine syrup, White pine
Potassium guaiacolsulfonate
Sodium citrate
Terpin hydrate preparations: Terpin hydate, Terpin hydrate elixir
Tolu preparations: Tolu, Tolu balsam, Tolu balsam tincture
Turpentine oil (spirits of turpentine) (topical/inhalant)

a. *Ammonium chloride.* The Panel concludes that ammonium chloride is safe in the dosage range used as an expectorant but there are insufficient data to permit final classification of its effectiveness for OTC use as an expectorant.

(1) *Safety.* Clinical experience has confirmed that ammonium chloride is safe in the dosage ranges used as an expectorant.

Several studies have documented the occurrence of severe acidosis, especially in patients with renal or hepatic dysfunction (Refs. 1 through 3). Most of these occurred with doses in excess of 6 to 8 gm per day where it was being used as a diuretic. Relman, Shelburne and Talman (Ref. 4) reported two near fatal cases following ingestion of huge amounts, 82 gm taken in a 48 hour period; while Ticktin, Fazekas and Evans (Ref. 5) described a case report of hepatic coma precipitated by 6 gm in a patient with congestive heart failure. At the dose ranges of 250 to 500 mg 4 to 6 times daily, which is the customary dose as an expectorant, the major adverse reaction has been nausea and emesis (Ref. 6).

(2) *Effectiveness.* There are no well-controlled studies documenting the effectiveness of ammonium chloride as an expectorant. No objective evaluations have been reported. Partially controlled subjective studies (Ref. 7) showed no significant change in either sputum volume or viscosity. Several investigators (Refs. 8 through 10) felt that sputum was more fluid and easier to raise when given at doses 0.3 gm every 2 hours, and Basch, Holinger and Poncher (Ref. 11) reported a decrease in visocity and pH (acidity) in patients with damaged bronchial tubes and infection.

(3) *Proposed dosage.* Adult oral dosage is 300 mg every 2 to 4 hours. Children 6 to under 12 years oral dosage is 150 mg every 2 to 4 hours. Children 2 to under 6 years oral dosage is 75 mg every 4 hours. For children under 2 years, there is no recommended dosage except under the advice and supervision of a physician.

(4) *Labeling.* The Panel recommends the Category I labeling for expectorant active ingredients. (See part IV. paragraph B.1. above—Category I Labeling.) In addition, the Panel recommends the following specific labeling: *Warnings.* (i) "*Caution:* This product must be taken with adequate amounts (½ to 1 glass) of fluids with each dose".

(ii) "Do not take this product if you have heart trouble or chronic kidney or lung disease except under the advice and supervision of a physician".

(5) *Evaluation.* Data to demonstrate effectiveness as an expectorant will be required in accordance with the guidelines set forth below for testing expectorant drugs. (See part IV. paragraph C. below—Data Required for Evaluation.)

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b. *Beechwood creosote.* The Panel concludes that beechwood creosote is safe in the dosage range used as an expectorant but there are insufficient data to permit final classification of its effectiveness for OTC use as an expectorant.

(1) *Safety.* Clinical experience has confirmed that beechwood creosote in the usual dosages contained in lozenges or cough mixtures for expectorant activity is safe.

Creosote is a distillate of wood tar and has a smokey color and a pungent taste. Dosages in excess of 4 gm 3 times daily produces giddiness, dimness of vision, circulatory collapse, convulsions and coma (Ref. 1). Because of the taste, it is normally given well-diluted (Ref. 2). Occasional adverse gastrointestinal side effects are mentioned in one report but are poorly documented (Ref. 3). Based on the available data and the presence of beechwood creosote on the market for many years, the Panel concludes that this ingredient is safe for OTC use.

(2) *Effectiveness.* There are no well-controlled studies documenting the effectiveness of beechwood creosote as an expectorant. No controlled or partially controlled studies were submitted to the Panel documenting its effectiveness as an expectorant. Only one reference (Ref. 3) was found that reported some increase of respiratory tract fluid (RTF) in animals given high dosages but the authors expressed doubt as to the applicability of these data to man. According to the standard compendia (Refs. 1 and 4), an average dose of beechwood creosote is 250 mg 3 or 4 times a day. In the two submissions to the Panel listing creosote, the dosages are 3.29 mg/lozenge and 33 mg/15 ml every 3 hours (Ref. 5). This 40 to 80-fold difference in dosage (3.29 mg/lozenge, 8 dosages daily) appears illogical and there is no evidence to indicate that creosote is effective in such low doses. The Panel concludes that further studies are needed to determine effectiveness.

(3) *Proposed dosage.* Adult oral dosage is 250 mg every 4 to 6 hours not to exceed 1,500 mg in 24 hours. Children 6 to under 12 years oral dosage is 125 mg every 4 to 6 hours not to exceed 750 mg in 24 hours. Children 2 to under 6 years oral dosage is 62.5 mg every 4 to 6 hours not to exceed 375 mg in 24 hours. For children under 2 years, there is no recommended dosage except under the advice and supervision of a physician.

(4) *Labeling.* The Panel recommends the Category I labeling for expectorant active ingredients. (See part IV. paragraph B.1. above—Category I Labeling.)

(5) *Evaluation.* Data to demonstrate effectiveness as an expectorant will be required in accordance with the guidelines set forth below for testing expectorant drugs. (See part IV. paragraph C. below—Data Required for Evaluation.)

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c. *Benzoin preparations (compound benzoin tincture, tincture of benzoin) (inhalant).* The Panel concludes that tincture of benzoin and compound benzoin tincture are safe in the dosage ranges used as an expectorant but there are insufficient data to permit final classification of its effectiveness for OTC use as an expectorant.

(1) *Safety.* Clinical experience has confirmed that benzoin tincture and compound benzoin tincture are safe in the dosage ranges used in boiling water as a steam inhalant for expectorant purposes.

Benzoin is the balsamic resin obtained from *Styrax benzoin* Dryander or Styrax paralleloneurus Perkins, known in commerce as Sumatra Benzoin or from *Styrax* tonkinensis (Pierre) Craib ex Hartwich, or other species of the Section *Anthostyrax* of the genus Styrax, known in commerce as Siam benzoin (San. *Styraceae*) (Ref. 1).

Benzoin is used in preparing official preparations, e.g., compound benzoin tincture, United States Pharmacopeia XIX (Ref. 1) and benzoin tincture, National Formulary XI (Ref. 2). Compound benzoin tincture contains 74 to 80 percent alcohol and is prepared by a maceration process incorporating benzoin, aloe, storax and tolu balsam using alcohol as a menstruum (Ref. 1). Benzoin tincture contains 75 to 83 percent alcohol and is also prepared by macerating benzoin, the final product being a 20 percent solution of benzoin (Ref. 2). These preparations are used topically as a protectant and antiseptic and by steam inhalation as an expectorant (Refs. 3 and 4). It is generally recognized as safe when administered by steam inhalation in accordance with recommended concentrations. The alcohol content would be responsible for the major toxic signs and symptoms arising from oral administration of the tincture (Ref. 5).

(2) *Effectiveness.* There are no well-controlled studies documenting the effectiveness of tincture of benzoin and compound benzoin tincture as an expectorant.

Although compound benzoin tincture and benzoin tincture have been advocated and used for generations as a component of steam inhalations to promote an expectorant action, no studies demonstrating this effect have been found in the literature or OTC submissions.

(3) *Proposed dosage.* Dosage for adults and children 2 to under 12 years of age is as follows: Add 1 teaspoonful of compound benzoin tincture or benzoin tincture to a pint of water in a hot steam vaporizer, bowl or washbasin. Breathe in vapors during the period of medicated steam generation. May be repeated 3 times daily. For children under 2 years, there is no recommended dosage except under the advice and supervision of a physician.

(4) *Labeling.* The Panel recommends the Category I labeling for expectorant active ingredients. (See part IV, paragraph B.1. above—Category I Labeling.) In addition, the Panel recommends the following specific labeling: *Warning:* "For use by steam inhalation only. Do not take by mouth".

(5) *Evaluation.* Data to demonstrate effectiveness as an expectorant will be required in accordance with the guidelines set forth below for testing expectorant drugs. (See part IV. paragraph C. below—Data Required for Evaluation.)

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d. *Camphor (topical/inhalant)*. The Panel concludes that camphor is safe in the dosage ranges used when applied topically or as an inhalant but there are insufficient data to permit final classification of its effectiveness for topical or inhalant OTC use as an expectorant.

(1) *Safety*. Clinical experience has confirmed that camphor (topical/inhalant) is safe in the dosage ranges used as an expectorant.

Camphor is a local irritant producing skin redness when rubbed on the skin. However, when not vigorously applied, it may produce a feeling of coolness on the skin as does menthol. It acts similarly on the respiratory tract. Taken orally in small doses it produces a feeling of warmth and comfort in the stomach but in larger doses it is irritating and can cause nausea and vomiting. Camphor also has a mild local anesthetic action and its application to the skin may be followed by numbness. The systemic effects are primarily related to stimulation of the central nervous system. The ingestion of solid camphor by children can cause convulsions (Ref. 1). As little as 0.75 gm of camphor equivalent to a teaspoonful of linament of camphor or camphorated oil that contains 20 percent camphor has been fatal to a child. Commercially available ointments containing mixtures of volatile substances for use as decongestants or antitussives contain about 5 percent camphor. Since it is conceivable that ingestion of a sufficient amount of such a preparation could produce toxic effects in a young child, a suitable warning should be present on the label. The ingestion of 2 gm of camphor generally produces toxic effects in an adult although up to 1.5 oz has been ingested with recovery (Ref. 2).

(2) *Effectiveness*. There are no well-controlled studies documenting the effectiveness of camphor (topical/inhalant) as an expectorant. Its effectiveness is uncertain due to lack of properly controlled studies of the substance by itself.

A standard text indicates that camphor may have a slight expectorant action (Ref. 1). Well-controlled specific studies to document this effect have not been found in the literature.

(3) *Proposed dosage*. Dosage for adults and children 2 to under 12 years is as follows: (i) For topical use as a 5 percent ointment preparation: To be rubbed on the throat, chest, and back as a thick layer. The area of application may be covered. However, clothing should be left loose about the throat and chest to help the vapor rise to reach the nose and mouth. Applications may be repeated up to 3 times daily.

(ii) For steam inhalation use as a 7 percent solution: 1 tablespoonful of solution per quart of water is added directly to the water in a hot steam vaporizer, bowl, or washbasin; or 2 teaspoonfuls of solution per pint of water are added to an open container of boiling water. Breathe in vapors during the period of medicated steam generation. May be repeated 3 times daily.

(iii) For topical use as a lozenge 0.02 to 15 mg: Allow lozenge to dissolve slowly in mouth. May be repeated every ½ to 1 hour.

For children under 2 years, there is no recommended topical or inhalant dosage except under the advice and supervision of a physician.

(4) *Labeling*. The Panel recommends the Category I labeling for expectorant active ingredients. (See part IV. paragraph B.1. above—Category I Labeling.) In addition, the Panel recommends the following specific labeling: (i) For topical ointment use: *Warning*: "For external use only. Do not take by mouth or place in nostrils".

(ii) For steam inhalation use: *Warning*: "For steam inhalation only. Do not take by mouth".

(5) *Evaluation*. The Panel made the following recommendations: (i) For topical ointment use: Data to demonstrate effectiveness will be required in accordance with the guidelines set forth below for testing expectorant drugs. (See part IV. paragraph C. below—Data Required for Evaluation.)

(ii) For steam inhalation use: Data to demonstrate effectiveness will be required in accordance with the guidelines set forth below for testing expectorant drugs. (See part IV. paragraph C. below— Data Required for Evaluation.)

(iii) For topical use as a lozenge: Data to demonstrate effectiveness will be required in accordance with the guidelines set forth below for testing expectorant drugs. (See part IV. paragraph C. below—Data Required for Evaluation.)

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e. *Eucalyptol/eucalyptus oil (topical/inhalant)*. The Panel concludes that eucalyptol/eucalyptus oil is safe in the dosage ranges used when applied topically or as an inhalant but there are insufficient data to permit final classification of its effectiveness for topical or inhalant OTC use as an expectorant.

(1) *Safety*. Clinical experience has confirmed that eucalyptol/eucalyptus oil (topical/inhalant) is safe in the dosage ranges used as an expectorant.

Eucalyptus oil is about 70 percent active eucalyptol. Fatalities have followed doses of the oil as small as 3.5 ml although recovery has occurred after doses of 20 and even 30 ml. Symptoms include epigastric burning with nausea and vomiting, vertigo, ataxia, muscle weakness and stupor (Refs. 1 and 2). A study of 223 subjects in which an ointment containing several volatile substances, including eucalyptus oil 1.3 percent, was applied for 48 hours to areas of intact skin under a patch and to abraded skin, revealed no instances of irritation, inflammation, wheal or hives following the period of exposure (Ref. 3). A study of ten subjects who received application of an ointment containing several volatile substances including eucalyptus oil 1.3 percent to their trunks 3 times daily for 3 weeks, then 1 week off followed by another 1 week of treatment, revealed no local reactions during this subsequent challenge phase (Ref. 4). A study of infants and children with respiratory infection who received an ointment containing a mixture of volatile oils, including eucalyptus oil 1.3 percent, applied to the chest and neck demonstrated no adverse effect from inhaled vapors by that route of administration on the rate of clearing of laryngeal edema (Ref. 5). In another study, the vapors were produced by placing a liquid mixture of volatile substances, including eucalyptus oil 1.7 percent, in the water of a hot steam vaporizer and administered via inhalation. Exaggerated use studies in adults and children, i.e., exposure for several hours to higher than recommended exposure concentrations either due to sitting in closer proximity to the vaporizer or placing 2 to 5 times the recommended dose of the volatile substance in the vaporizer, were not associated with irritating or toxic effects (Refs. 6 and 7).

A series of studies assessing buccal safety and overt side effects from lozenges containing a mixture of volatile oils was conducted in over 300 subjects (Refs. 8 through 11). Lozenges containing up to 5.5 mg eucalyptus oil were dissolved in the mouth every hour for 8 hours on 2 successive days. Mild erythema of the buccal mucosa and tongue was observed but did not differ appreciably from the response to dissolving lozenge sugar base without volatile oils. Incidence of gastrointestinal symptoms did not differ from control either (Refs. 8 through 11).

An aerosolized dosage form of volatile substances including 1 percent eucalyptus oil has also been utilized for treatment of nasal congestion. In humans, such aerosol sprays have been generally safe when used as directed but there have been reports of deaths from deliberate sniffing abuse, particularly when the subject inhales from a plastic bag into which the material has been sprayed (Ref. 12). Furthermore, one commercial preparation containing a particular solvent (1,1,1-trichloroethane) was recently recalled from the market due to potential hazards of this substance (Ref. 13).

(2) *Effectiveness*. There are no well-controlled studies documenting the effectiveness of eucalyptol/eucalyptus oil (topical/inhalant) as an expectorant. Its effectiveness is uncertain due to lack of properly controlled studies of the substance by itself.

Eucalyptus oil is traditionally assumed to have an expectorant action by virtue

of direct stimulation of bronchial secretory cells following inhalation (Ref. 14). In one study, eucalyptus oil was administered via steam inhalation to rabbits and respiratory tract fluid collected (Ref. 15). At normal doses eucalyptus oil did not increase the volume or decrease the specific gravity of the collected fluids. Larger doses were required for eucalyptus oil to produce this effect, and these doses led to local inflammation and several animal deaths (Ref. 15). In a later study, this group administered eucalyptol by stomach tube to anesthetized animals. Eucalyptol was shown to be an expectorant in rats, guinea pigs, rabbits, cats, and dogs. The effect was not influenced by section of the afferent gastric nerves. From this observation the authors concluded that eucalyptol does not act by a reflex mechanism in the stomach but directly upon the secretory cells of the respiratory tract (Ref. 16). Conclusive studies to confirm this expectorant property in humans are lacking.

(3) *Proposed dosage.* Dosage for adults and children 2 to under 12 years is as follows: (i) For topical use as a 1.3 percent ointment preparation: To be rubbed on the throat, chest, and back as a thick layer. The area of application may be covered. However, clothing should be left loose about the throat and chest to help the vapors rise to reach the nose and mouth. Applications may be repeated up to 3 times daily.

(ii) For steam inhalation use as a 1.7 percent solution: 1 tablespoonful of solution per quart of water is added directly to the water in a hot steam vaporizer, bowl or washbasin; or 2 teaspoonfuls of solution per pint of water are added to an open container of boiling water. Breathe in vapors during the period of medicated steam generation. May be repeated 3 times daily.

(iii) For topical use as a lozenge 0.2 to 15.0 mg: Allow lozenge to dissolve slowly in mouth. May be repeated every ½ to 1 hour.

For children under 2 years, there is no recommended topical or inhalant dosage except under the advice and supervision of a physician.

(4) *Labeling.* The Panel recommends the Category I labeling for expectorant active ingredients. (See part IV. paragraph B.1. above—Category I Labeling.) In addition, the Panel recommends the following specific labeling: (i) For topical ointment use: *Warning:* "For external use only. Do not take by mouth or place in nostrils".

(ii) For steam inhalation use: *Warning:* "For steam inhalation only. Do not take by mouth".

(5) *Evaluation.* The Panel made the following recommendations: (1) For topical ointment use: Data to demonstrate effectiveness will be required in accordance with the guidelines set forth below for testing expectorant drugs. (See part IV. paragraph C. below—Data Required for Evaluation.)

(ii) For steam inhalation use: Data to demonstrate effectiveness will be required in accordance with the guidelines set forth below for testing expectorant drugs. (See part IV. paragraph C. below—Data Required for Evaluation.)

(iii) For topical use as a lozenge: Data to demonstrate effectiveness will be required in accordance with the guidelines set forth below for testing expectorant drugs. (See part IV. paragraph C. below—Data Required for Evaluation.)

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f. Glyceryl guaiacolate. The Panel concludes that glyceryl guaiacolate is safe in the dosage ranges used as an expectorant but there are insufficient data to permit final classification of its effectiveness for OTC use as an expectorant.

(1) *Safety.* Clinical experience has confirmed that glyceryl guaiacolate is safe in the dosage ranges used as an expectorant.

Acute and chronic toxicity studies in animals demonstrated no adverse pathologic findings (Ref. 1). A number of studies in humans also demonstrates the safety of glyceryl guaiacolate over a wide range of dosages (Refs. 2, 3, and 4). Carter (Ref. 5) administered 100 mg/lb of body weight to 18 children with cerebral palsy for periods of 1 month. One child complained of loss of appetite and two exhibited nausea and vomiting. All laboratory data remained within normal limits (blood chemistry, complete blood count, and urine). An epidemiological study (Ref. 6) indicates that glyceryl guaiacolate is one of the most widely used medications with few reported adverse reactions.

Inhibition of in vitro platelet aggregation in the blood with prolongation of coagulation time of activated plasma has been described (Refs. 7 and 8) but appears to have no clinical significance (Refs. 9 and 10). Glyceryl guaiacolate may interfere with certain laboratory tests, such as 5-hydroxyindoleacetic acid and vanillyl mandelic acid (Refs. 11 and 12) which are employed as screening tests for carcinoid (hormone secreting) tumors and pheochromocytoma.

(2) *Effectiveness.* There are no well-controlled studies documenting the effectiveness of glyceryl guaiacolate as an expectorant.

Earlier animal studies, in which glycerol guaiacolate was reported as increasing respiratory tract fluid (Refs. 13 and 14) were subsequently revised to indicate that the expectorant activity of glyceryl guaiacolate occurred only at extremely high doses (Ref. 15).

There have been a large number of clinical studies in man. Even in the early studies, the lack of acceptable standard techniques for evaluation was recognized. These studies can be subdivided into subjective uncontrolled reports (Refs. 16, 17, and 18) claiming effectiveness in the management of cough and good patient acceptance; subjective controlled or semicontrolled studies (Refs. 19 and 20) claiming superiority of glyceryl guaiacolate (100 to 200 mg 4 times daily) over placebo with respect to ease of raising sputum, and ameliorating the unproductive cough and objective controlled studies in which the flow properties of sputum were measured or the clearance rates of inhaled radioactive tracer particles were determined. Hirsch et al. (Ref. 2) and Hirsch, Viernes and Kory (Ref. 21) found glyceryl guaiacolate at dosages of 800 to 1,600 mg daily to be no more effective than placebo in lowering sputum consistency, increasing sputum volume or improving ventilatory function. The subjective ease of expectoration was also no different than with placebo. Chodosh (Ref. 22) and Chodosh, Medici and Enslein (Ref. 23), on the other hand, dispute these findings and in a letter to the editor of *Chest*, Chodosh and Medici (Ref. 24) claim improvement in subjective symptoms, pulmonary function tests, and sputum stickiness (adhesiveness) with 2.4 gm glyceryl guaiacolate daily. Perhaps the most striking point in his discussion is that even at 2.4 gm daily the most significant changes were noted only after 10 days

although trends could be detected at 7 days. The report by Thomson, Pavia and McNicol (Ref. 25) showing a significantly faster clearance of inhaled radioactive particles over the first 5 hours with glyceryl guaiacolate in single doses of 200 mg as compared to placebo in bronchitic patients in a double-blind crossover study is of special interest both in the evaluation of glyceryl guaiacolate and as an objective type of assessment for expectorant drugs. This is a new approach to the study of expectorants and is objective in design. If results can be confirmed, it may represent a "breakthrough" in methodology.

If glyceryl guaiacolate requires 7 to 10 days to begin to demonstrate a significant expectorant effect, it is obviously not suited for OTC use where rapid relief of symptoms in a self-limited illness of relatively short duration is desired. It should be emphasized that the study by Thomson, Pavia and McNicol (Ref. 25) suggesting drug activity is a single study that has not been confirmed by any other investigator. Hirsch et al. (Ref. 2) and Hirsch, Viernes and Kory (Ref. 21), employing another objective controlled method of study, were unable to demonstrate effectiveness. It would appear that the contradictory results of these two studies cancel each other out in a manner of speaking.

A recent subjective double-blind study was submitted in which there were 121 patients in a placebo group and 118 who received 200 mg every 6 hours for a period of 72 hours (Ref. 26). Statistical analysis of the data was reported as showing a significant reduction in cough frequency and intensity in the patients on glyceryl guaiacolate. However, this conclusion by a subjective method of evaluation is unacceptable as a claim for suppression of cough frequency or intensity in keeping with the Panel's statement that effectiveness of a drug with respect to antitussive activity must be assessed by objective techniques, such as cough-counting methods as described in the section under evaluation of antitussives. (See part III. paragraph C. below—Data Required for Evaluation.)

In addition, this study reported that glyceryl guaiacolate administration was associated with the production of a significantly thinner sputum and was effective in increasing sputum volume and facilitating the raising of secretions in patients with a productive cough. In examining the data, it was noted that one investigator in this multidisciplinary study submitted two separate studies with a total of 76 subjects which accounted for approximately one-third of the total subject population. Another investigator presented data that showed no significant difference from placebo and a third investigator showed a significant trend in favor of glyceryl guaiacolate. Because of the conflicting results of the different investigators on this study and the likelihood that the data from the single investigator referred to above would bias the results of the study when all the information is pooled, serious questions are raised as to the validity of the study. Retrospective analysis of the data with respect to smoking showed that there was no bias introduced by the incidence of smoking of the subjects (Ref. 27).

There are a number of controlled, objective studies with combinations of theophylline and glyceryl guaiacolate in reversible airway obstruction studies but these were not relevant to its expectorant acivity.

There is considerable dispute as to the effective dosage. From the more recent reports in the literature it would appear to be 2 to 4 times higher than the customary dose of 100 mg.

(3) *Proposed dosage.* Adult oral dosage is 200 to 400 mg every 4 hours not to exceed 2400 mg in 24 hours. Children 6 to under 12 years oral dosage is 100 to 200 mg every 4 hours not to exceed 1200 mg in 24 hours. Children 2 to under 6 years oral dosage is 50 to 100 mg every 4 hours not to exceed 600 mg in 24 hours. For children under 2 years, there is no recommended dosage except under the advice and supervision of a physician.

(4) *Labeling.* The Panel recommends the Category I labeling for expectorant active ingredients. (See part IV. paragraph B.1. above—Category I Labeling.)

(5) *Evaluation.* Data to demonstrate effectiveness will be required in accordance with the guidelines set forth below for testing expectorant drugs. Effectiveness to be established by only one additional controlled study which in view of the difficulty in obtaining objective criteria for such evaluations, could be a well-designed subjective study. (See part IV. paragraph C. below—Data Required for Evaluation.)

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(27) OTC Volume 040280.

g. *Ipecac syrup.* The Panel concludes that ipecac syrup is safe in the dosage ranges used as an expectorant but there are insufficient data to permit final classification of its effectiveness for OTC use as an expectorant.

(1) *Safety.* Clinical experience has confirmed that syrup of ipecac is safe in the dosage ranges used as an expectorant but there are no known studies to substantiate this belief. There are no known studies on the toxicity of ipecac as a single ingredient. The chief alkaloids of ipecac, emetine and cephaeline, are very toxic (Ref. 1). It has been shown that when these alkaloids are given parenterally (by injection), they are cumulative with toxic effects on the heart, liver, kidney, intestinal tract, and skeletal muscle (Refs. 1 and 2); however,

when given orally, there is no information on the absorption of small doses from the gastrointestinal tract, or on the cumulative effects of repeated administration. In view of possible cumulative effects from oral administration, the Panel recommends a 1-week time limit of use for any ipecac preparation except when given under the advice and supervision of a physician.

Based on the long history of use and on the available data, the Panel concludes that when given in small doses as proposed below, ipecac syrup is safe for OTC use.

(2) *Effectiveness.* In large doses, ipecac is an emetic. However, in the subemetic dosages used as an expectorant, its effectiveness is questionable. There are no acceptable clinical studies to substantiate its use as an expectorant.

Practically all the work with ipecac was done more than 2 decades ago. Animal studies using varying preparations of ipecac indicate that this drug may increase the flow of respiratory tract fluid (Refs. 3 through 7). Several controlled studies in humans with chronic cough did not demonstrate that ipecac was effective as an expectorant (Refs. 8, 9, and 10). In one study, bronchial fluid collected by bronchoscopic drainage revealed lowered viscosity following ipecac administration (Ref. 11). The available data is insufficient to make a determination that ipecac is effective, and the Panel recommends further study.

(3) *Proposed dosage.* Adult oral dosage is 0.5 to 1 ml of a syrup containing not less than 123 mg and not more than 157 mg of total ether-soluble alkaloids of ipecac per 100 ml 3 to 4 times daily. Children 6 to under 12 years oral dosage is 0.25 to 0.5 ml of syrup 3 to 4 times daily. For children under 6 years, there is no recommended dosage except under the advice and supervision of a physician.

(4) *Labeling.* The Panel recommends the Category I labeling for expectorant active ingredients. (See part IV. paragraph B.1. above—Category I Labeling.) In addition, the Panel recommends the following specific labeling: *Warning:* "Do not give this product to children under 6 years except under the advice and supervision of a physician".

(5) *Evaluation.* Data to demonstrate effectiveness will be required in accordance with the guidelines set forth below for testing expectorant drugs. (See part IV. paragraph C. below—Data Required for Evaluation.)

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h. *Menthol/peppermint oil (topical/inhalant).* The Panel concludes that menthol/peppermint oil is safe in the dosage ranges used when applied topically or as an inhalant but there are insufficient data to permit final classification of its effectivness for topical or inhalant OTC use as an expectorant.

(1) *Safety.* Clinical experience has confirmed that menthol/peppermint oil (topical/inhalant) is safe in the dosage ranges used as an expectorant.

Menthol is the chief constituent of peppermint oil, comprising not less than 50 percent. It may be obtained by distillation of the oil or by synthesis (Ref. 1). Toxic effects with an excess ingestion of peppermint oil or mentholated products can include abdominal pain, nausea, vomiting and symptoms of central nervous system depression, such as dizziness, staggering gait, slowed respiration, flushed face, sleepiness, and coma (Refs. 2 and 3). The fatal oral dose of menthol itself in man is about 2 gm (Ref. 4). Topically applied menthol produces a cooling sensation presumably due to stimulation of the cold sensory receptors, whereas higher concentrations have irritant properties. In one study, a 20 percent solution of menthol in oil rubbed on to the skin induced an intense and lasting cooling sensation followed by numbness with slight burning and skin redness. A 0.5 precent solution applied to the nasal or oral mucosa was subjectively irritating whereas a 0.2 percent solution was judged nonirritating (Ref. 5). A study of 223 subjects in which an ointment containing several volatile substances including menthol 2.8 percent was applied for 48 hours to areas of intact skin under a patch and to abraded skin revealed no instances of inflammation, wheal, hives, or primary irritation following the period of exposure (Ref. 6). Repeated topical application of mentholated products has been reported to give rise to hypersensitivity reactions, including contact dermatitis (Ref. 4). A study of ten subjects who received an application of an ointment containing several volatile substances including menthol 2.8 percent to their trunks 3 times daily for 3 weeks, then 1 week off, followed by another week of treatment, revealed no local reactions during this subsequent challenge phase (Ref. 7). One study suggests that the incidence of hypersensitivity to menthol appears to increase with increased duration of use. This survey revealed an incidence of less than 1 percent menthol hypersensitivity in 542 patients using a mentholated ointment for less than 10 years, whereas an incidence of 3.4 percent hypersensitivity was seen in 414 patients using this type of a preparation for longer than 10 years (Ref. 8).

In infants and small children, nasal ointment or drops containing menthol may cause spasm of the glottis and cases of dangerous asphyxiation have been reported in infants following local application of menthol. For this reason a warning against the topical application of menthol-containing products directly to the nostrils of infants has been recommended (Refs. 4 and 9). A study of infants and children with respiratory infection who received an ointment containing a mixture of volatile oils including 2.8 percent menthol applied to the chest and neck demonstrated no adverse effect from the inhaled vapors by that route of administration on the rate of clearing of laryngeal inflammation. In this study 35 children, 23 under 2 years of age, with respiratory infection received only standard forms of therapy, e.g., antibiotics and fluids, while 37 children, 30 under 2 years of age, received standard therapy plus the mentholated ointment applied to the chest and neck. Laryngoscopic examination revealed comparable rates of clearing of laryngeal inflammation (Ref. 10).

A liquid mixture of volatile substances including 3.66 percent menthol is placed in the water of a hot steam vaporizer and administered via inhalation. A number of studies involving nearly 900 subjects in which this mixture was administered at recommended doses was not associated with significant complaints of subjectively perceived adverse effects (Refs. 11 through 23). Exaggerated-use studies in adults and children, i.e., exposure for several hours to higher than recommended exposure concentrations either due to sitting in closer proximity to the vaporizer or placing 2 to 5 times the recommended dose of the volatile substance in the vaporizer was not associated with irritating or toxic effects (Refs. 24 and 25).

In two studies, 40 healthy subjects asked to dissolve two candy-base lozenges, each lozenge containing 1.36 mg of menthol together with other volatile oils, every 20 minutes for 2 hours exhibited no adverse effects with the exception of one report of nausea and vomiting. This was attributed to a dislike for the wild cherry flavor of the lozenge (Refs. 26 and 27). In a group of 70 healthy subjects, 50 adults and 20 children ages 8 to 12, half dissolved a menthol-eucalyptus lozenge containing

9.62 mg menthol and 5.55 mg eucalyptus oil every 4 to 8 hours on 2 successive days, the other half dissolved the cough drop base without the aromatics. In this intensive dosage schedule, a slightly larger number of subjects demonstrated mild irritation of the oral mucosa on day 1 and day 2, but there were no differences between the two groups in the severity of irritation or residual findings after day 2. No systemic complaints were reported (Ref. 28). A similar study using a lozenge formulation containing menthol 8.14 mg and eucalyptus oil 4.625 mg versus a lozenge base without volatile substances produced comparable results (Ref. 29).

An aerosolized dosage form of volatile substances including 1 percent menthol has also been utilized for treatment of nasal congestion and cough symptoms. Rats exposed to acute overdoses of the spray in a confined chamber for 6 hours revealed no untoward behaviorial responses or airway tissues abnormality upon autopsy examination (Ref. 30). A group of four monkeys were exposed to 200 gm per day of the aerosol, i.e., 2 gm of menthol total dose in divided doses over an 8-hour period for 14 consecutive days in a confined chamber. Eye irritation was the only pharmacotoxic sign observed during the study (Ref. 31). In humans, such aerosol sprays have been generally safe when used as directed, but there have been reports of deaths from deliberate sniffing abuse, particularly when the subject inhales from a plastic bag into which the material has been sprayed (Ref. 32). Furthermore, one commercial preparation containing a particular solvent, 1,1,1-trichloroethane, was recently recalled from the market due to potential hazards of this substance (Ref. 33).

(2) *Effectiveness.* There are no well-controlled studies documenting the effectiveness of menthol/peppermint oil (topical/inhalant) as an expectorant. Its effectiveness is uncertain due to lack of properly controlled studies of the substance by itself.

The local anesthetic effect of menthol vapor has been the justification for including menthol in topically administered ointments and lozenges for alleviation of cough. In a crossover study involving 16 subjects the effects of a 2.8 percent mentholated petrolatum ointment applied to the chest of the subjects was compared to an ointment containing several volatile substances including 2.8 percent menthol, and to petrolatum in suppressing a citric acid aerosol-induced cough. A combination ointment containing menthol induced a significant decrease in cough counts at all challenge times from ½ hour through 2 hours, averaging about 20 percent decrease at the ½ and 1 hour intervals, whereas the single ingredient menthol ointment yielded a significant decrease in cough counts just at the ½ and 1 hour intervals, averaging about 10 percent reduction. The petrolatum yielded no significant decrease in cough counts compared with base line (Ref. 34). Similar results with the combination ointment containing 2.8 percent menthol were obtained in two additional induced-cough studies conducted by the same investigator (Refs. 34 and 35).

A single-blind crossover cough-counting study of 27 patients exhibiting stabilized chronic cough utilized twice daily chest applications of either the ointment containing several volatile substances including 2.8 percent menthol, an ointment containing 1.3 percent eucalyptus oil, or petrolatum base. Neither the ointment mixture nor the eucalyptus oil ointment induced a significant decrease in cough counts compared to placebo after the morning application, but a significant 20 percent cough-count reduction compared to placebo was obtained following the afternoon dose of the ointment mixture. An average reduction in cough counts of about 10 percent compared to placebo was noted following the afternoon dose of eucalyptus oil ointment, but this was not statistically significant (Ref. 36).

A liquid mixture of volatile substances added to the water of a hot steam vaporizer and administered via inhalation contained menthol 3.66 percent, camphor 7 percent, eucalyptus oil 1.7 percent, and tincture of benzoin 5 percent. Three crossover studies compared the effects of this volatile substance containing liquid in steam, 1 tablespoonful per quart of water, to steam alone in suppressing coughs artifically induced by the citric acid aerosol technique. In each case both steam and medicated steam induced a statistically significant reduction in cough counts during the period of administration. In two of the studies the cough reduction with the medicated steam was statistically greater than with steam alone and persisted beyond the period of actual administration to the subject (Refs. 37, 38, and 39). Subjective evaluation studies of adults and infants having cough associated with respiratory infection demonstrated statistically significant antitussive effectiveness of the volatile substances in steam, 1 tablespoon per quart of water, and of steam alone. In some of these studies the effect of the medicated steam was judged statistically superior to the steam alone (Refs. 40, 41, and 42).

The variety of lozenge preparations containing a mixture of volatile substances including menthol have been studied for their ability to suppress citric acid aerosol induced cough in normal subjects. Since each of these lozenge preparations contain different concentrations of menthol and other volatile substances, the results of the study will be individually summarized. The general study format involved an unblinded crossover design in which a group of cough-standardized normal subjects were tested with each of two lozenge formulations, the active formulation and its vehicle control, against cough artificially induced by the citric acid aerosol technique. Two studies involved lozenges in which menthol was the principal active ingredient and consequently represent an indication of the effectiveness of this mode of administering menthol to suppress cough. One of the studies involving 16 subjects used a lozenge containing menthol 2.64 mg and peppermint oil 2.29 mg plus benzyl alcohol 5.76 mg. The active formulation produced significant cough reductions at the 10- to 40-minute challenge periods, reaching a peak of 30 to 35 percent at the 10- and 20-minute intervals whereas the control lozenge produced a significant reduction of 15 to 20 percent at the 10- and 20-minute intervals only (Ref. 43). The other study of ten subjects utilizing a lozenge containing menthol 1.13 mg plus citric acid flavoring produced greater cough reduction than the control lozenge at the 10- through 30-minute challenge periods although both the active and control lozenges in this study produced cough reductions at these time intervals (Ref. 44).

Two studies involving a total of 40 subjects used similar active formulations consisting of menthol 9.6 mg and eucalyptus oil 5.5 mg per lozenge. In these studies the active formulation produced significant cough reductions at the 10- to 40-minute challenge periods, reaching a peak of 25 to 35 percent reduction at the 10- and 20-minute intervals whereas the control lozenge produced a significant reduction of 10 to 15 percent maximum at only the 10-minute challenge (Refs. 45 and 46). In a study of nine subjects receiving lozenge doses of menthol 1.5 mg and eucalyptol 0.35 mg, elevated citric acid thresholds of 130 to 146 percent of control for 3 to 5 hours after dosing were obtained, although a placebo control lozenge was not utilized in this study for comparison (Ref. 47). Another study of 20 subjects utilizing a formulation of menthol 2.78 mg, eucalyptus oil 0.77 mg plus smaller amounts of camphor, thymol, and tolu balsam, produced significant cough reductions at the 10- through 40-minute challenge periods, reaching a peak of 35 percent reduction at the 10- and 20-minute intervals whereas a control lozenge produced a significant reduction of 11 to 17 percent maximum at the 10- and 20-minute challenge periods only (Ref. 48). Similar results were obtained in 16 subjects using an active formulation containing menthol, eucalyptus oil, camphor, thymol, and tolu balsam present in about ½ the amounts utilized in the preceding study (Ref. 49).

(3) *Proposed dosage.* Dosage for adults and children 2 to under 12 years is as follows: (i) For topical use as a 2.8 percent ointment preparation: To be rubbed on the throat, chest, and back as a thick layer. The area of application may be covered. However, clothing should be left loose about the throat and chest to help the vapors rise to reach the nose and mouth. Applications may be repeated up to 3 times daily.

(ii) For steam inhalation use as a 3.66 percent solution: 1 tablespoonful of solution per quart of water is added directly to the water in a hot steam vaporizer, bowl, or washbasin; or 2 teaspoonfuls of solution per pint of water are added to an open container of boiling water. Breathe in vapors during the period of medicated steam generation. May be repeated 3 times daily.

(iii) For topical use as a lozenge 1.0 to 12 mg: Allow lozenge to dissolve

slowly in mouth. May be repeated every ½ to 1 hour.

For children under 2 years, there is no recommended topical or inhalant dosage except under the advice and supervision of a physician.

(4) *Labeling.* The Panel recommends the Category I labeling for expectorant active ingredients. (See part IV. paragraph B.1. above—Category I Labeling.) In addition, the Panel recommends the following specific labeling: (i) For topical ointment use: *Warning:* "For external use only. Do not take by mouth or place in nostrils".

(ii) For steam inhalation use: *Warning:* "For steam inhalation only. Do not take by mouth".

(5) *Evaluation.* The Panel made the following recommendations: (i) For topical ointment use: Data to demonstrate effectiveness will be required in accordance with the guidelines set forth below for testing expectorant drugs. (See part IV. paragraph C. below—Data Required for Evaluation.)

(ii) For steam inhalation use: Data to demonstrate effectiveness will be required in accordance with the guidelines set forth below for testing expectorant drugs. (See part IV. paragraph C. below—Data Required for Evaluation.)

(iii) For topical use as a lozenge: Data to demonstrate effectiveness will be required in accordance with the guidelines set forth below for testing expectorant drugs. (See part IV. paragraph C. below—Data Required for Evaluation.)

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1. *Pine tar preparations (extract white pine compound, pine tar, syrup of pine tar, compound white pine syrup, white pine).* The Panel concludes that pine tar preparations are safe in the dosage range used as expectorants but effectiveness at those dosages has not been established.

(1) *Safety.* Clinical experience has confirmed that the pine tar preparations are safe in the dosage ranges used as expectorants. The above preparations are administered orally for an expectorant activity. The active ingredient is pine tar, a product obtained by the destructive distillation of wood of various species of pine, usually "Pinus palustrus." It is a viscid blackish-brown noncrystalline

liquid. It has a turpentine-like odor and a sharp taste of organic decomposition. It has been used mainly for diseases of the skin, being slightly irritating, antiseptic, and with local anesthetic properties.

The Panel is unaware of any studies to evaluate the safety of pine tar. It is probably safe in the recommended doses since it has been used for decades without any recorded reports of adverse effects (Refs. 1 through 4).

(2) *Effectiveness.* There are no well-controlled studies documenting the effectiveness of pine tar preparations as expectorants. The use of pine tar preparations as expectorants appears to be based solely on tradition. There is no evidence that they are effective as an expectorant when taken orally.

(3) *Proposed dosage.* Adult oral dosage is 1.6 mg every 3 to 4 hours. Children 6 to under 12 years oral dosage is 0.8 to 1.0 mg every 3 to 4 hours. Children 2 to under 6 years oral dosage is 0.4 to 0.5 mg every 3 to 4 hours. For children under 2 years, there is no recommended dosage except under the advice and supervision of a physician.

(4) *Labeling.* The Panel recommends the Category I labeling for expectorant active ingredients. (See part IV. paragraph B.1. above—Category I Labeling.)

(5) *Evaluation.* Data to demonstrate effectiveness as an expectorant will be required in accordance with the guidelines set forth below for testing expectorant drugs. (See part IV. paragraph C. below—Data Required for Evaluation.)

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j. *Potassium guaiacolsulfonate.* The Panel concludes that potassium guaiacolsulfonate is safe in the dosage ranges used as an expectorant but there are insufficient data to permit final classification of its effectiveness for OTC use as an expectorant.

(1) *Safety.* Clinical experience has confirmed that potassium guaiacolsulfonate is safe in the dosage ranges used as an expectorant. There is no evidence of toxicity in the available literature. Information is sparse, and there is no documentation of adverse reactions.

(2) *Effectiveness.* There are no well-controlled studies documenting the effectiveness of potassium guaiacolsulfonate as an expectorant. While subjective studies would indicate that it is ineffective as an expectorant (Refs. 1 and 2), potassium guaiacolsulfonate has been used empirically, for many decades, in expectorant mixtures. Connell, et al. (Ref. 3) showed no change in water content of the respiratory tract of rats. Two papers cited that potassium guaiacolsulfonate is not metabolized to guaiacol (Refs. 1 and 2).

Many of the submissions to the Panel listed preparations containing potassium guaiacolsulfonate at 80 to 90 mg/5 ml with 1 tablespoonful recommended as the adult dose (240 to 270 mg per dose). One study, however, employed an adult dose of 500 mg (Ref. 4). Based on the scanty evidence, the Panel concludes that there is a wide dose range with no specific optimum level for expectorant activity.

(3) *Proposed dosage.* The Panel is unable to determine a proposed dosage. The Panel concludes that the pharmaceutical industry should consult with the Food and Drug Administration as to a suitable proposed dosage for testing. Otherwise, the Panel recommends that each drug manufacturer evaluate the dosage as labeled on the manufacturer's marketed product(s).

(4) *Labeling.* The Panel recommends the Category I labeling for expectorant active ingredients. (See part IV. paragraph B.1. above—Category I Labeling.)

(5) *Evaluation.* Data to demonstrate effectiveness will be required in accordance with the guidelines set forth below for testing expectorant drugs. (See part IV. paragraph C. below—Data Required for Evaluation.)

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k. *Sodium citrate.* The Panel concludes that sodium citrate is safe in the dosage range used as an expectorant but there are insufficient data to permit final classification of its effectiveness for OTC use as an expectorant.

(1) *Safety.* Clinical experience over more than a half a century has confirmed that sodium citrate is safe in the dose ranges used as an expectorant. It is mildly diuretic and, in larger doses, may be laxative. Gastric irritation can be produced if taken undiluted (Ref. 1).

(2) *Effectiveness.* There are no well-controlled studies documenting the effectiveness of sodium citrate as an expectorant. Goodman and Gilman (Ref. 1) states that the use of citrates as expectorants is mainly empirical and it is "probable that the water ingested with them is the basis for any beneficial effect." A similar preparation, potassium citrate was found to have very little effect upon the output of respiratory tract fluid in a dose as high as 0.4 gm/kg of body weight (Ref. 2).

(3) *Proposed dosage.* Adult oral dosage is 1.0 to 2.0 gm every 2 to 4 hours taken well diluted with at least ½ glass of water or fruit juice (Ref. 3). Children 6 to under 12 years oral dosage is 0.5 to 1.0 gm every 2 to 4 hours diluted as above with water or fruit juice. Children 2 to under 6 years oral dosage is 250 to 500 mg every 2 to 4 hours diluted as above with water or fruit juice. For children under 2 years, there is no recommended dosage except under the advice and supervision of a physician.

(4) *Labeling.* The Panel recommends the Category I labeling for expectorant active ingredients. (See part IV. paragraph B.1. above—Category I Labeling.) In addition, the Panel recommends the following specific labeling: *Warnings:* (i) "*Caution:* This product must be taken with adequate amounts of fluids (½ to 1 glass) with each dose".

(ii) "*Caution:* Do not take this product if you have heart trouble or kidney disease except under the advice and supervision of a physician".

At smaller amounts, less than the proposed doses above, sodium citrate has been employed in liquid mixtures for its mild saline taste. In these instances, it is not classified as an active ingredient, and no labeling claim should be made for it since it is being used as a flavoring agent.

(5) *Evaluation.* Data to demonstrate effectiveness will be required in accordance with the guidelines set forth below for testing expectorant drugs. (See part IV. paragraph C. below—Data Required for Evaluation.)

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(2) Boyd, E. M., B. Palmer and B. Pearson, "Is There Any Advantage in Combining Several Expectorant Drugs in a Compound Cough Mixture?" *Canadian Medical Association Journal*, 54:216–220, 1946.

(3) *Remington's Practice of Pharmacy*, 12th Ed., Edited by Martin, E. W., p. 814, 1961.

l. *Terpin hydrate preparations (terpin hydrate, terpin hydrate elixir).* The Panel concludes that terpin hydrate is safe in the dosage ranges used as an expectorant but there are insufficient data to permit final classfication of its effectiveness for OTC use as an expectorant.

(1) *Safety.* Clinical experience has confirmed that terpin hydrate is safe in the dosage ranges used as an expectorant.

A few papers noted gastrointestinal distress from dosages of 340 to 680 mg/24 hours, with nausea and vomiting (Refs. 1 and 2). Elixir terpin hydrate has a high alcoholic content of approximately 42 percent which could be subject to alcohol abuse (Ref. 3). The Panel has recognized the potential for such abuse as stated in a previous section of this document. (See part II. paragraph G. above—Drug Misuse and Abuse.) Based on the available data and its long history of use, the Panel concludes that terpin hydrate is safe for OTC use in the dosages discussed below. However, because of the high alcohol content required to formulate and manufacture elixir terpin hydrate, the Panel recommends that elixir terpin hydrate not be used in children younger than 12 years.

(2) *Effectiveness.* There are no well-controlled studies documenting the effectiveness of terpin hydrate as an expectorant. The majority of papers in the literature question the effectiveness of terpin hydrate and indicate that it is probably harmless and useless (Refs. 2 through 5). Two papers indicate that at a dose of 300 mg 4 times daily, it had a "loosening effect," but these were subjective evaluations (Refs. 6 and 7). The Panel concludes that the information available is not sufficient to determine that terpin hydrate is effective as an expectorant.

(3) *Proposed dosage.* Adult oral dosage is 200 mg every 4 hours not to exceed 1200 mg in 24 hours. The elixir should not be given to children under 12 years of age but terpin hydrate by itself or in a nonalcoholic mixture can be used. Children 6 to under 12 years oral dosage is 100 mg every 4 hours not to exceed 600 mg in 24 hours. Children 2 to under 6 years oral dosage is 50 mg every 4 hours not to exceed 300 mg in 24 hours. For children under 2 years, there is no recommended dosage except under the advice and supervision of a physician.

(4) *Labeling.* The Panel recommends the Category I labeling for expectorant active ingredients. (See part IV. paragraph B.1. above—Category I Labeling.) In addition, the Panel recommends the following specific labeling: *Warnings.* (i) "May produce nausea and vomiting".

(ii) For elixir products containing 42 percent alcohol: *"Caution:* This product contains 42 percent alcohol and should not be given to children under 12 years except under the advice and supervision of a physician".

(5) *Evaluation.* Data to demonstrate effectiveness will be required in accordance with the guidelines set forth below for testing expectorant drugs. (See part IV. paragraph C. below—Data Required for Evaluation.)

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(2) Hirsch, S. R., "The Use of Expectorants," *Wisconsin Medical Journal*, 70:153–156, 1971.

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(4) Richerson, H. B., "Expectorants," *Journal of the Iowa Medical Society*, 58:875–876, 1965.

(5) Grzybowski, S., "Cough Medicines," *Canadian Medical Association Journal*, 92: 619–620, 1965.

(6) Rose, I., "The Ineffectiveness of Expectorants," *Canadian Medical Association Journal*, 69:494–495, 1953.

(7) Boyd, E. M., "Expectorants and Respiratory Tract Fluid," *Pharmacological Reviews*, 6:521–542, 1954.

m. *Tolu preparations (tolu, tolu balsam, tolu balsam tincture).* The Panel concludes that tolu balsam is safe in the dosage range used as an expectorant but there are insufficient data to permit final classification of its effectiveness for OTC use as an expectorant.

(1) *Safety.* Clinical experience has confirmed that tolu preparations are safe in the dosage ranges used as expectorants. Tolu balsam can be considered safe in the dosages used for expectorant activity when administered orally or by inhalation.

There is no documentation as to toxicity at the dose levels in general usage in man. One report (Ref. 1) states that huge doses, "1,000 times that recommended," when given by inhalation produced an acute inflammation of the tracheal lining in rabbits.

(2) *Effectiveness.* There are no well-controlled studies documenting the effectiveness of tolu preparations as expectorants. There is no evidence that tolu balsam possesses expectorant activity.

Several reports by Boyd and his coworkers (Refs. 2 through 4) are conflicting and consist for the most part of statements rather than data from studies, i.e., "Syrup of Tolu did have an expectorant action." Certain volatile oils (Friar's balsam) stimulate the output of respiratory tract fluids (RTF) or bronchial secretions (Ref. 3). In another paper (Ref. 4), the author states that inhalation by animals of therapeutic doses of certain volatile oils (Friar's balsam) has no effect upon respiratory tract fluids. A standard text states that tolu balsam syrup is "widely employed as a vehicle for expectorant drugs but has no specific virtue for this purpose" (Ref. 5). The Panel takes cognizance of the fact that tolu balsam has been used for many decades as an ingredient in steam inhalations and in oral expectorant mixtures but concludes that there are insufficient data to determine the effectiveness of tolu balsam as an expectorant.

(3) *Proposed dosage.* Adult oral dosage is 50 mg every 2 to 3 hours. Children 6 to under 12 years oral dosage is 25 mg every 2 to 3 hours. Children 2 to under 6 years oral dosage is 12.5 mg every 2 to 3 hours. For children under 2 years, there is no recommended dose except under the advice and supervision of a physician.

(4) *Labeling.* The Panel recommends the Category I labeling for expectorant active ingredients. (See part IV. paragraph B.1. above—Category I Labeling.)

(5) *Evaluation.* Data to demonstrate effectiveness will be required in accordance with the guidelines set forth below for testing expectorant drugs. (See part IV. paragraph C. below—Data Required for Evaluation.)

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n. *Turpentine oil (spirits of turpentine) (topical/inhalant).* The Panel concludes that turpentine oil is safe in the dose ranges used when applied topically or as an inhalant but there are insufficient data to permit final classification of its effectiveness for topical or inhalant OTC use as an expectorant.

(1) *Safety.* Clinical experience has confirmed that turpentine oil is safe when applied topically or used as an inhalant in the dose ranges used as an expectorant. The Panel concludes that oil of turpentine is safe when applied externally or vaporized in boiling water as a steam inhalant. However, the Panel has determined elsewhere in this document that it is not safe for OTC use when used orally as an expectorant. (See part IV. paragraph B.2.f. above—Turpentine oil (spirits of turpentine) (oral).)

Oil of turpentine is a volatile oil consisting of a mixture of pinenes derived from the oleoresin obtained from Pinus palustrus. Nelson et al. (Ref. 1) found exposure to a vapor of 420 to 560 mcg/l acceptable to most of their human subjects. The threshold for industrial exposure for 8 hours has been set at 560 mcg/l. The maximum concentration obtainable with a currently marketed OTC preparation is 36 mcg/l (Refs. 2 and 3). No histological evidence of pulmonary lesions were seen in mice and rats exposed to lethal concentrations of turpentine vapors (Ref. 4). Inhalation of 300 mcg/l of turpentine vapor by mice for 15 minutes did not influence the electrocardiogram, respiratory minute volume, pulmonary airway, resistance or compliance (Ref. 5). One study in mice using a mixture of volatile oils, one of which was turpentine, showed a decrease in pulmonary antibacterial activity (Ref. 6). Two other studies showed no change when the mixture was used (Refs. 7 and 8).

In several studies in children and infants suffering from minor breathing discomforts associated with the "common cold," no side effects that were drug related were observed when a medicated steam was administered (Refs. 9 through 13). Turpentine has been widely used as a part of a mixture of volatile oils for many years, with approximately two complaints per million packages purchased (Ref. 14).

(2) *Effectiveness.* There are no well-controlled studies documenting the effectiveness of turpentine oil as an expectorant when applied externally or vaporized in boiling water as a steam inhalant due to a lack of objective measurement studies of the substance by itself.

(3) *Proposed dosage.* Dosage for adults and children 2 to under 12 years is as follows: (i) For topical use as a 4.0 percent ointment preparation: To be rubbed on the throat, chest, and back as a thick layer. The area of application may be covered. However, clothing should be left loose about the throat and chest to help

the vapor rise to reach the nose and mouth. Applications may be repeated up to 3 times daily.

(ii) For steam inhalation use a 5.5 percent solution: 1 tablespoonful of solution per quart of water is added directly to the water in a hot steam vaporizer, bowl, or washbasin; or 2 teaspoonfuls of solution per pint of water are added to an open container of boiling water. Breathe in vapors during the period of medicated steam generation. May be repeated 3 times daily.

For children under 2 years, there is no recommended topical or inhalant dosage except under the advice and supervision of a physician.

(4) *Labeling.* The Panel recommends the Category I labeling for expectorant active ingredients. (See part IV. paragraph B.1. above—Category I Labeling.) In addition, the Panel recommends the following specific labeling: (i) For topical ointment use: *Warning:* "For external use only. Do not take by mouth or place in nostrils".

(ii) For steam inhalation use: *Warning:* "For steam inhalation only. Do not take by mouth".

(5) *Evaluation.* The Panel made the following recommendations: (i) For topical ointment use: Data to demonstrate effectiveness will be required from only one additional well-controlled cough-counting objective study in patients with coughs due to respiratory disease in accordance with the guidelines set forth below for testing expectorant drugs. (See part IV. paragraph C. below—Data Required for Evaluation.)

(ii) For steam inhalation use: Data to demonstrate effectiveness will be required in accordance with the guidelines set forth below for testing expectorant drugs. (See part IV. paragraph C. below—Data Required for Evaluation.)

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(14) OTC Volume 040279.

Category III Labeling

The Panel concludes that substantiation by additional data is required before statements regarding duration of action, e.g., "all day", "all night", "for hours" will be acceptable. Such statements must specify in the labeling the number of hours of relief claimed. The statements must be verified by appropriate documentation.

C. DATA REQUIRED FOR EVALUATION

The Panel has agreed that the protocols recommended in this document for the studies required to bring a Category III drug into Category I are in keeping with the present state of the art and do not preclude the use of any advances or improved methodology in the future.

1. *Principles in the design of an experimental protocol for testing expectorant drugs.* a. *General principles.* The effectiveness of an expectorant preparation is based on its ability to facilitate the removal of sputum from the respiratory passageways and thus clear the airway of retained secretions. By aiding in the removal of these secretions and through a soothing effect on irritated mucous membranes, it will indirectly ease the act of coughing. While the ease in raising secretions may seem simple to measure and assess, there are, at present, no suitable objective methods for evaluating this. This difficulty stems, in part, from a lack of basic knowledge concerning the biochemical and physiochemical nature of respiratory tract secretion in various respiratory diseases, as well as the changes produced by expectorant drugs, and the lack of evidence as to which property of sputum correlates best with ease of expectoration. Because of this, the subjective evaluation of the patient must be relied upon the assessment of the drug's expectorant activity.

b. Selection of patients. Based upon the method of study to be used, two types of patients may be selected. One patient type who would be chosen for a crossover study could include subjects with chronic cough due to chronic pulmonary disease such as chronic bronchitis, pulmonary emphysema, inactive pulmonary tuberculosis, etc., and whose condition is relatively stable with no evidence of intercurrent infection that would affect cough or character of the sputum. A second patient type could include subjects with an acute upper respiratory infection, such as an acute bronchitis or tracheobronchitis, in which a dry nonproductive cough is a prominent feature. Because the production of respiratory secretions may be influenced by other systems, such as the circulation, patients with congestive heart failure or significant renal or hepatic disease must be excluded. Furthermore, every effort must be made to maintain the same relative state of hydration and activity, and drugs must be prohibited that may affect sputum, such as the anticholinergics and antihistamines. While nonsmokers would be preferable as subjects, the smoking habits of patients must be carefully documented and maintained at the same level throughout the clinical trials. No smoking would be permitted during the actual recording sessions. While impractical to control, the effect of environmental factors such as temperature, humidity, and degree of air pollution should be recognized.

c. *Methods of study* (1) *Double-blind crossover design in patients with chronic lung disease.* A suitable period for baseline studies must be performed prior to the administration of the test drugs. During this period, the following subjective indices will be noted: Ease of expectoration; character of the cough (whether productive or not); frequency of coughing; and breathing comfort, i.e., heavy, noisy, rattling, etc. Additional help in evaluating effectiveness may be provided by some objective indices such as: The volume and dry weight of sputum collections over a given time (12 to 24 hours); the character and color of the sputum raised; and some measure of its flow properties, such as viscosity or consistency. If a cough suppression claim is to be substantiated, an objective cough-counting study must be done as discussed under antitussives. (See part III. paragraph C. above—Data Required for Evaluation.) Following baseline studies, similar observations are obtained during the administration of the drug and placebo which must be indistinguishable from each other, randomized, and provided at a dose and time sequence recommended for OTC use. This type of study would require approximately 3 weeks, 1 week on each preparation and 1 week for the baseline data.

(2) *A randomized double-blind design in patients with acute upper respiratory infections.* Groups of patients would receive either a placebo or the drug under study in a similar dose and time interval as recommended for OTC use over a period of 3 to 5 days. Similar observations, as discussed above, would be obtained where possible to evaluate effectiveness, but no prior baseline period would be obtainable with this model and most of the data would be limited to the subjective indices. Patient diaries would be kept in which the type of symptoms, their duration and severity as well as adverse reactions would be recorded daily.

d. *Interpretation of data.* Evidence of drug effectiveness is required from a minimum of three positive studies based on the results of three different investigators or laboratories. At least one of the three studies must be in patients with chronic pulmonary disease. Approximately 20 to 30 patients will be required for the crossover study described above. Because of the marked variability in cough and sputum production in acute respiratory disease from day to day together with the spontaneous waning of

symptoms as part of its natural history, a much larger number of patients, possible 75 or more, must be studied for this group. The subjective indices to be evaluated can be scored for statistical analysis, with a p value of 0.05 or less (95 percent confidence level) being acceptable as evidence of a drug effect when compared with placebo.

All data submitted to the Food and Drug Administration must present both favorable and any unfavorable results.

e. *Evaluation of safety.* Tests for safety of expectorant ingredients not reviewed by this Panel should involve the usual animal studies and observations in man relevant to various organs and system, i.e., cardiovascular, respiratory, renal, hepatic, cerebral, and hematologic. Of special note insofar as expectorant drugs may be concerned are such factors as carcinogenicity, effect on clotting mechanisms, thyroid function, electrolyte and acid-base balance, in addition to the general areas mentioned above.

V. Bronchodilators

A. General Discussion

Bronchodilators are agents used for the symptomatic treatment of the wheezing and shortness of breath associated with asthma. These agents are used to overcome the spasm that causes narrowing of the bronchial air tubes. These drugs are also used but are much less effective in relieving the shortness of breath of chronic bronchitis and emphysema. The drugs most commonly used as bronchodilators are some sympathomimetics (sympathomimetic amines), theophylline, and theophylline salts. The Panel has classified these two major forms of bronchodilators, i.e., sympathomimetic amines and theophyllines, as distinct pharmacologic groups. The sympathomimetic amines and theophyllines work well when given together, but it is preferable that the dose of each should be individualized for each patient (Ref. 1).

The sympathomimetics may be given orally (ephedrine and methoxyphenamine), by aerosol inhalation (epinephrine solution), by rectal installation, by injections under the skin or into the muscle of the upper arm or buttocks, and in some situations under medical supervision sympathomimetics may be used under the tongue.

Theophyllines are usually given by oral administration but they may also be given, under medical supervision, by the rectal route or by intravenous injection. The oral preparations of theophylline are not affected by food in the stomach (Ref. 2). Excessive doses result in high blood levels which cause nausea and vomiting. Individuals metabolize these drugs at different rates. Therefore, some patients require only a relatively small dose of the drug while others require quite large doses for a satisfactory effect. Occurrence of nausea or vomiting will indicate when the dose of drug is excessive. Only one of the theophyllines and only one route of administration should be used at a time because of the additive effects of these drugs.

Adverse reactions associated with the sympathomimetic bronchodilators consist primarily of those affecting the cardiovascular and central nervous systems. These drugs may cause arrhythmias, hypertension, dizziness, tremor, nervousness, and sleeplessness. They may also cause a rise in blood sugar concentration and in older men they may cause slowing or even obstruction to the urinary stream. Because of these possible reactions, the drugs should be used with caution in individuals with cardiac disease, hypertension, hyperthyroidism, diabetes, or prostatic enlargement.

The theophyllines given orally or rectally may produce nausea and vomiting which, in extreme cases, may result in dehydration and shock.

Theoretically a combination product containing a theophylline drug and a sympathomimetic to be taken by mouth, for example, as a tablet, should be very effective and convenient. However, to obtain the most effective bronchodilation, the dose of theophylline should be individualized because of individual variation in the metabolic breakdown of theophyllines (Ref. 3).

The Panel is concerned that in a patient who is a rapid metabolizer of theophylline, a fixed-dose of a theophylline and a sympathomimetic in an oral combination product might have reduced effectiveness because of a low theophylline dose. If the number of dosage units, e.g., combination tablets taken, is increased to provide an effective theophylline dose, the dose of sympathomimetic might be excessive and cause side effects. Conversely, in a patient who is a slow metabolizer of theophylline, the standard dose of an oral combination product of theophylline and a sympathomimetic might produce theophylline toxic effects. If the number of combination tablets is decreased to avoid these side effects, then the dose of sympathomimetic might be so low as to have a low effectiveness.

Therefore, it would appear that single ingredient preparations containing either a theophylline or a sympathomimetic would be both more effective and have increased safety as compared to combination products.

Although the bronchodilators are generally safe for OTC use at recommended dosage and are effective in relieving the shortness of breath caused by bronchospasm, the Panel emphasizes that these preparations should not be used unless a diagnosis of asthma has been made by a physician and a dosage schedule of OTC medicine has been established by a physician.

Patients with asthma may also require prescription drugs which may have serious dangers and side effects and there is, then, an added need for continued medical supervision.

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B. Categorization of Data

1. *Category I conditions under which bronchodilator ingredients are generally recognized as safe and effective and are not misbranded.*

Category I Active Ingredients

The Panel has classified the following bronchodilator active ingredients as generally recognized as safe and effective and are not misbranded:

Sympathomimetic amines

Ephedrine preparations: Ephedrine, Ephedrine hydrochloride, Ephedrine sulfate, Racephedrine hydrochloride

Epinephrine preparations (inhalant): Epinephrine, Epinephrine bitartrate, Epinephrine hydrochloride (racemic)

Methoxyphenamine hydrochloride

Theophyllines

Theopyhilline preparations: Aminophylline, Theophylline anhydrous, Theophylline calcium salicylate, Theophylline sodium glycinate

a. *Ephedrine preparations (ephedrine, ephedrine hydrochloride, ephedrine sulfate, racephedrine hydrochloride).* The Panel concludes that ephedrine preparations are safe and effective for OTC use as bronchodilators as specified in the dosage section discussed below.

(1) *Safety.* Ephedrine, when absorbed systemically, has effects both on the brain (central) and on nerve endings (peripheral) (Ref. 1). In clinical usage, the central effects are stimulatory and include tenseness, nervousness, tremor and sleeplessness. Peripheral effects include bronchodilatation, and possibly shrinkage of mucous membranes (decongestion), although this has not been documented. Other peripheral effects include awarness of heartbeat and rapid heart beat accompanied usually by some elevation of blood pressure. However, a study by Dulfano and Glass on 26 asthmatics between the ages of 28 and 61 years showed that a single dose of 25 mg had no significant effect on either heart rate or blood pressure (Ref. 2). Another recent study of the cardiovascular effects of 25 mg ephedrine in 20 asthmatics showed there was only a modest increase in heart rate up to 11 beats per minute as a maximum, and the systolic and diastolic blood pressure showed no significant change (Ref. 3). In spite of these findings, the cardiovascular and central effects appear to set limits on dosage, limits which vary widely among patients as judged by clinical experience. Loss of appetite and nausea also occur in some patients. Difficulty in urination may occur in older males who might have enlarged prostate glands. The drug, under these circumstances, exacerbates obstruction to urine flow by causing spasm of the outlet of the bladder. Overdosage results in exaggeration of the side effects which patients describe as disagreeable and can usually be depended upon to prevent overuse or abuse. Ordinary doses may cause marked and potentially dangerous increases in blood pres-

sure in patients taking drugs containing monoamine oxidase (MAO) inhibitors.

(2) *Effectiveness.* The bronchodilator effects of ephedrine taken by mouth are slow in onset, probably 15 to 25 minutes, and probably persist for 2 to 3 hours, based on the Panel's clinical observations. The drug is less effective as a bronchodilator than epinephrine, and its usefulness is limited to the milder forms of asthma.

A dose of 25 mg by mouth given to asthmatic patients prevented the bronchospasm induced by various chemicals (Ref. 4). The fall in vital capacity induced by histamine was prevented to the extent of 40 percent and that by methacholine to the extent of 32 percent (Ref. 4). Although based on objective measurements, this study does not seem to have been rigorously planned or executed as judged by today's standards.

In a double-blind comparison of 24 mg ephedrine and a combination of 24 mg ephedrine and 130 mg theophylline, measurements including specific airway resistance, vital capacity, and FEV_1 (forced expiratory volume in one second—a measurement related to airway obstruction, the higher the figure the better the airflow and the less the obstruction in the air tubes) showed that ephedrine significantly decreased the first and increased the last two over a period of 2 hours, an effect that was enhanced and prolonged by the presence of theophylline (Ref. 5). Each preparation also contained 8 mg of phenobarbital. Although a placebo was not included, these findings carried out with sophisticated objective measurements, strongly support a bronchodilator effect for ephedrine.

In a study comparing ephedrine and terbutaline in 26 asthmatics, it was shown that 25 mg ephedrine resulted in a maximal change of FVC 11 percent, FEV_1 18 percent, MVV 17 percent, MMF 25 percent, and MEFR 24 percent over the controlled figures. The improvement in the pulmonary function tests were statistically significant between 120 and 240 minutes after taking a single dose. The results were similar to 2.5 mg terbutaline but were less than the effect of 5.0 mg terbutaline (Ref. 2).

In a recent study of 20 patients with asthma, 25 mg ephedrine showed effective bronchodilation for up to 4 hours (the respiratory function tests of FVC, FEV_1 and airway resistance were used) (Ref. 3).

(3) *Dosage.* Adult oral dosage is 12.5 to 25 mg not more often than every 4 hours not to exceed 150 mg in 24 hours. Children 2 to under 12 years oral dosage is identified in the labeling section discussed below under professional labeling. For children under 2 years, there is no recommended dosage except under the advice and supervision of a physician. There is insufficient information as to the possible toxic effect of ephedrine in this age group.

The Panel strongly recommends that ephedrine be available as scored tablets containing 12.5 mg and 25 mg ephedrine per tablet to permit flexibility in dosage.

(4) *Labeling.* The Panel recommends the Category I labeling for bronchodilator active ingredients. (See part V. paragraph B.1. below—Category I Labeling.) In addition the Panel recommends the following specific labeling: *Warnings.* (i) *"Caution:* Do not continue to take this product but seek medical assistance immediately if symptoms are not relieved within 1 hour or become worse".

(ii) "Nervousness, tremor, sleeplessness, nausea and loss of appetite may occur".

(iii) "Do not take this product if you have heart disease, high blood pressure, thyroid disease, diabetes, or difficulty in urination due to enlargement of the prostate gland".

(iv) *Drug Interaction Precaution.* "Do not take this product if you are presently taking a prescription antihypertensive or antidepressant drug containing a monoamine oxidase inhibitor".

(v) "Do not give this product to children under 12 years except under the advice and supervision of a physician".

(vi) *Professional labeling.* The Panel recommends that labeling provided to health professionals (but not to the general public) may contain the following additional dosage information: Children 6 to under 12 years oral dosage is 6.25 to 12.5 mg not more often than every 4 hours not to exceed 75 mg in 24 hours. Children 2 to under 6 years oral dosage is 0.3 to 0.5 mg/kg of body weight not more often than every 4 hours not to exceed 2 mg/kg of body weight in 24 hours.

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b. *Epinephrine preparations (epinephrine, epinephrine bitartrate, epinephrine hydrochloride (racemic)) (inhalant).* The Panel concludes that epinephrine is safe and effective for OTC use as a bronchodilator as specified in the dosage section discussed below.

(1) *Safety.* Wide use of epinephrine aerosols for temporary relief of spasm that causes narrowing of air tubes has been attended by few and mild side effects. However, one early report by Benson and Perlman (Ref. 1) raised the possibility that excessive use of epinephrine aerosols caused serious harm to the lining of the air tubes, resulting in an increase in air tube secretions which in turn predisposes to infection and collapse of small areas of the lungs. Alternative causes for these changes were not seriously considered. The report was retrospective and it found that a greater number of deaths occurred in users of epinephrine aerosols, 48 of 648 (7.4 percent) as compared with 22 of 1,588 nonusers (1.4 percent). The possibility that the users might have had a more severe illness than nonusers was not considered and might well explain the findings.

In a study of 86 patients with various types of cardiac involvement and 16 patients with uncontrolled diabetes who inhaled aqueous epinephrine from a nebulizer (Ref. 2), no untoward effects developed following administration of many times the dose considered to be effective in asthma, nor were there significant changes in pulse rate, blood pressure, electrocardiogram, or blood sugar level. The authors conclude that the presence of cardiovascular disease or diabetes is not a contraindication to the use of d,l-epinephrine (racemic) or l-epinephrine (levorotatory) by inhalation.

Epinephrine aerosol was used for many years before its safety was seriously questioned. The question arose because of an increase in the number of deaths among those using a chemically related drug, isoproterenol, a prescription drug, which also caused aggravation of the airway obstruction in some patients.

The reports of an increase in deaths from isoproterenol had their origin in England (Ref. 3). A possible explanation was that the preparation used there had a concentration of isoproterenol 5 times greater than that used in Sweden, Australia, and the United States, where no such increase in deaths had been noted (Ref. 4). It was inferred that the high concentration of isoproterenol accounted for the increased deaths. Deaths decreased when a lower concentration of isoproterenol was used.

Aggravation of the obstructive abnormality clearly occurs in some patients with asthma following administration of isoproterenol (Ref. 5). This may be due to some fraction of absorbed isoproterenol being converted to a metabolite which could predispose to causing spasm of air tubes (Ref. 6).

It has been further observed (Ref. 7) that isoproterenol by inhalation, while producing bronchodilation, may simultaneously cause a small and usually clinically insignificant fall in blood oxygen level. That this has not been observed with epinephrine by inhalation may merely reflect the small amount of interest in this drug in the years since techniques for making the necessary measurements have become readily available, but the tests have not been done.

It is unlikely that these observations of toxicity concerning isoproterenol are relevant in judging the safety of epinephrine by inhalation. Epinephrine stimulates both alpha and beta receptors (Ref. 8) and would be expected to have a local constrictor effect on blood vessels in the lungs as it does in subcutaneous tissue, an effect expected to limit systemic absorption of the administered

drug. Isoproterenol is predominantly a stimulator of beta receptors (Ref. 8) and would be expected to cause vascular dilatation and systemic absorption of the administered drug. The relative therapeutic advantage or disadvantage of this difference between the two drugs is unknown and needs further study.

Since the isoproterenol adverse reactions are not known to bear on the safety of epinephrine by inhalation and since these postulated hazards would appear to be avoidable by using low concentrations and by instructing the patient by appropriate labeling, epinephrine by inhalation is judged by the Panel to be a safe preparation for OTC use.

One additional difficulty may arise which applies to all sympathomimetic drugs self-administered by inhalation for relief of asthma. A patient with severe and worsening obstructive pulmonary disease may obtain very temporary relief and this relief may give a false sense of security. Under such circumstances the patient may postpone calling a physician or going to a hospital until his disease has reached life-threatening severity and the suggested labeling in this document takes this possibility into account. The safety of propellants used in these preparations has not been reviewed by this Panel because they are considered to be pharmaceutical necessities which should be reviewed independently by the Food and Drug Administration. The side effects of sympathomimetics are worsened by monoamine oxidase inhibitors which prevent the breakdown of these drugs.

(2) *Effectiveness.* A number of letters from experts in the field of respiratory and allergic disease attest to the safety and effectiveness of inhaled aerosolized epinephrine (Ref. 9). In a double-blind study in asthmatics the timed vital capacity ($FEV_{0.5}$) was compared after metered inhalations of 0.125 mg epinephrine delivered per inhalation, 0.06 mg isoproterenol delivered per inhalation and a placebo (Ref. 10). The means taken to maintain experimental control are not described. Both epinephrine and isoproterenol gave significant increase within 15 minutes accompanied by symptomatic relief whereas the placebo gave little change. Side effects were not mentioned.

In a comparative study of several bronchodilator preparations including epinephrine but lacking a placebo (Ref. 11), epinephrine and the other preparations gave improved bronchial air flow in 12 asthmatic subjects. A specific bronchodilator effect for the preparations given seems highly probable but remains unestablished because of the lack of experimental control and the failure to include a placebo. In an uncontrolled study of the capacity of sympathomimetic drugs to prevent the fall in vital capacity and expiratory flow rate induced by methacholine and histamine (Ref. 12), inhaled epinephrine was effective.

(3) *Dosage.* Adults and children 4 years and above inhalation dosage is 1 to 3 inhalations of a 1 percent aqueous solution of l-epinephrine or the equivalent in a pressurized preparation not more often than every 3 hours, except under the advice and supervision of a physician. For children under 4 years, there is no recommended dosage except under the advice and supervision of a physician.

Children and adolescents should not have unsupervised access to this inhaler. There is the possibility of abuse of this material and possible adverse effects on the heart if excessively used.

(4) *Labeling.* The Panel recommends the Category I labeling for bronchodilator active ingredients. (See part V. paragraph B.1. below—Category I Labeling.) In addition, the Panel recommends the following specific labeling for preparations of epinephrine used by inhalation: *Warnings.* (i) "Do not take this product at higher than recommended doses except under the advice and supervision of a physician for it may cause nervousness and rapid heart beat".

(ii) *"Caution:* Do not continue to take this product but seek medical assistance immediately if symptoms are not relieved within 20 minutes or become worse".

(iii) "Do not take this product if you have heart disease or high blood pressure except under the advice and supervision of a physician".

(iv) *"Drug Interaction Precaution.* Do not take this product if you are presently taking a prescription antihypertensive or antidepressant drug containing a monoamine oxidase inhibitor".

(v) "Keep this product out of reach of children and adolescents because unsupervised access may cause abuse or possible adverse effects on the heart if excessively used".

(vi) "Do not give this product to children under 4 years except under the advice and supervision of a physician".

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c. *Methoxyphenamine hydrochloride.* The Panel concludes that methoxyphenamine hydrochloride is safe and effective for OTC use as a bronchodilator as specified in the dosage section discussed below.

(1) *Safety.* In a crossover study in 12 asthmatics, comparing 100 mg methoxyphenamine orally against 30 mg ephedrine sulfate, the types of side effects noted were similar although the frequency of complaints of side effects were only about one-half as frequent with methoxyphenamine. Other studies in asthmatic patients have also reported a lower incidence of side effects, particularly blood pressure changes and central nervous system stimulation, with comparable bronchodilator doses of methoxyphenamine and ephedrine (Refs. 1 through 4). Patients with a history of ephedrine intolerance were often able to tolerate 100 to 200 mg methoxyphenamine without experiencing the usual ephedrine-like side effects of nervousness, insomnia, tremor, and headache (Refs. 2 and 5). The most common side effects of methoxyphenamine appear to be dryness of mouth and mild anorexia (Ref. 4).

(2) *Effectiveness.* In asthmatic patients, oral methoxyphenamine 200 mg and ephedrine sulfate 30 mg offered comparable protection against decreased vital capacity and asthma-like symptoms due to parenterally administered histamine or methacholine (Refs. 1 and 6). Objective measurement studies in asthmatic patients have revealed an increase in vital capacity, up to 20 percent over a 4-hour period, following oral methoxyphenamine 100 to 200 mg (Refs. 2, 4, and 7). Of 61 asthmatic patients who took 100 mg every 4 hours, 37 obtained subjective relief of breathing difficulty. Six of the remaining 24 gained relief with a 200 mg dose every 4 hours (Ref. 2).

No data on the use of methoxyphenamine in children under 12 years are available and there has been little clinical experience with this drug in children. The Panel concludes that methoxyphenamine should not be used in children under 12 years until such time as satisfactory evidence of safety and effectiveness is available.

(3) *Dosage.* Adult oral dosage is 100 mg every 4 to 6 hours not to exceed 600 mg in 24 hours. For children under 12 years, there is no recommended dosage except under the advice and supervision of a physician.

(4) *Labeling.* The Panel recommends the Category I labeling for bronchodilator active ingredients. (See part V. paragraph B.1 below—Category I Labeling.) In addition, the Panel recommends the following specific labeling: *Warnings.* (i)

"*Caution:* Do not continue to take this product but seek medical assistance immediately if symptoms are not relieved within 1 hour or become worse."

(ii) "Nervousness, tremor, sleeplessness, nausea and loss of appetite may occur".

(iii) "Do not take this product if you have heart disease, high blood pressure, thyroid disease, diabetes or difficulty in urination due to enlargement of the prostate gland".

(iv) "'*Drug Interaction Precaution.* Do not take this product if you are presently taking a prescription antihypertensive or antidepressant drug containing a monoamine oxidase inhibitor".

(v) "Do not give this product to children under 12 years except under the advice and supervision of a physician".

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d. *Theophylline preparations (aminophylline, theophylline anyhydrous, theophylline calcium salicylate, theophylline sodium glycinate).* The Panel concludes that the theophylline preparations are safe and effective for OTC use as bronchodilators as specified in the dosage section discussed below when the dosage is based on the anhydrous theophylline equivalent.

(1) *Safety.* The most commonly encountered adverse effects of theophylline—anorexia, nausea, and vomiting—are apparently centrally mediated. Whether administered orally as uncoated tablets, by injection, or rectally, gastrointestinal symptoms in adults and children are usually negligible if whole blood levels of theophylline do not exceed 8 μg/ml (equivalent to plasma levels of 15 μg/ml). The corresponding plasma level is greater because theophylline does not enter the red blood cells (Refs. 1 through 7). Gastrointestinal symptoms were associated with orally administered aminophylline (theophylline ethlenediamine) when whole blood levels of theophylline exceeded 11 μg/ml (equivalent to plasma levels of 20 μg/ml) (Ref. 1).

Aminophylline administered as an uncoated tablet or theophylline as an alcoholic elixir is quite rapidly and reproducibly absorbed within 1 hour from an empty stomach. Thus, oral absorption and tissue response to a given concentration of theophylline as well as rate of renal excretion are fairly uniform from patient to patient. However, administration with meals or as an enteric coated tablet markedly contributes to slowing and variability in extent of absorption (Refs. 5 and 7). However, recent studies showed that food makes little difference in the absorption of theophylline provided the tablet has a satisfactory dissolution time (Refs. 8 and 9). Studies of theophylline indicate that variations between patients in their maintenance dose requirements are attributable to remarkable differences in the rate at which theophylline is metabolized. In one study of 83 patients, oral aminophylline dosage ranged from 400 to 3,200 mg/24 hours in order to maintain therapeutic blood levels. About 10 percent of patients receiving 300 mg every 4 hours for at least 48 hours experienced loss of appetite, nausea, and vomiting. Despite apparent variations in rate of theophylline metabolism between patients, each individual is internally quite stable in terms of rate of handling this drug so that it is possible to individualize a safe and effective dose for continued therapy (Ref. 1).

In children, oral doses of aminophylline of 4 to 5 mg/kg every 8 hours (80 percent of this dose for theophylline calculated as the free base) is recommended as generally devoid of undesirable side effects (Refs. 8 and 9). Severe toxicity in children may include vomiting with blood in the vomitus and dehydration, central nervous system stimulation leading to convulsions and coma, and cardiovascular collapse. The majority of literature reports of theophylline and aminophylline toxicity in children, and particularly those resulting in death, have been associated with use of aminophylline suppositories. Administered dosage of suppositories in reported toxicity cases ranged from a normal dosage of 10 mg/kg/24 hours to 75 mg/kg/36 hours (Refs. 8 and 10 through 29). Analysis of the cases of toxicity with recommended dosage of suppositories reveal the concurrent oral or parenteral administration of a theophylline preparation. Because of the toxicity potential from overdose unless the dose is individualized to the needs of a child on a mg/kg basis, the Panel believes that such OTC products should not contain labeling with a recommended dosage for children.

Aminophylline, due to its ethylenediamine content, may produce a contact-type dermatitis upon systematic administration to individuals previously sensitized to the topical application of ethylenediamine (Ref. 30).

(2) *Effectiveness.* Following intravenous aminophylline in a variety of patients with narrowing of the air tubes caused by spasm, the degree of objectively measured bronchodilation using measurements of air flow and airway resistance was correlated with whole blood levels of theophylline between 2 μg/ml up to a maximum effect at 8 μg/ml (equivalent to plasma levels of 3.6 to 14.5 μg/ml). A study of airway resistance changes in adult asthmatics following single oral doses of aminophylline demonstrated minimum whole blood levels of theophylline for maximal bronchodilator effect to range from 4.5 to 11 μg/ml (equivalent to plasma levels of 8 to 21 μg/ml). Because of patient variability in metabolism of aminophylline, the authors found that doses of 400 to 3,200 mg/24 hours, averaging 1,200 mg/24 hours, were needed to maintain therapeutically effective "trough" levels (middosing blood levels) of theophylline in the 5.5 to 11 μg/ml range. These authors recommend 300 mg aminophylline (240 mg anhydrous theophylline every 6 hours, 4 times daily (Ref. 1). Following 130 mg doses, blood levels at best reach 4.3 μg/ml (equivalent to plasma levels of 7.6 μg/ml) (Refs. 1, 3, and 31 through 33). Since the blood level attained and maintained in a given patient is dependent on drug metabolism rate, which varies among individuals, an OTC dose recommendation of 100 to 200 mg of anhydrous theophylline equivalent should help patients individualize the dose for optimal response yet minimize side effects.

The Panel recommends that scored compressed tablets in dosage units of 50 mg, 100 mg and 200 mg of anhydrous theophylline equivalent be made available for OTC use. The Panel is concerned that theophylline tablets be readily absorbed when ingested. All tablets must pass a satisfactory dissolution test. The Panel recommends that each tablet formulation be tested according to the procedures described in the United States Pharmacopeia XIX (Ref. 34). The tablets shall be considered satisfactory for OTC use if the quantity of theophylline dissolved within 15 minutes is not less than 50 percent of the labeled amount (based on anhydrous theophylline equivalent content) and the quantity of theophylline dissolved within 30 minutes is not less than 90 percent of the labeled amount of theophylline (based on anhydrous theophylline equivalent content) for any of the tablets tested. The resulting data should be submitted to the Food and Drug Administration prior to marketing.

A double-blind controlled study in 300 asthmatic children, ages 6 to 12, receiving 150 mg theophylline by mouth in plain capsules correlated with significant improvement as measured by pulmonary function tests with theophylline blood levels greater than 3.2 μg/ml (equivalent to plasma levels of 6 μg/ml) (Ref. 3).

A review of oral theophylline drugs lists the anhydrous theophylline equivalents in various proprietary preparations (Ref. 29). For purposes of standardization, the dosage recommendations of the Panel are based on anhydrous theophylline equivalent content.

(3) *Dosage.* Adult oral dosage based on the anhydrous theophylline equivalent is 100 to 200 mg every 6 hours not to exceed 800 mg in 24 hours. Children 2 to under 12 years oral dosage is identified in the labeling section discussed below under professional labeling. For children

under 2 years, there is no recommended dosage except under the advice and supervision of a physician.

The Panel recommends that scored compressed tablets in dosage units of 50 mg, 100 mg and 200 mg of anhydrous theophylline equivalent be made available for OTC use.

(4) *Labeling.* The Panel recommends the Category I labeling for bronchodilator active ingredients. (See part V. paragraph B.1. below—Category I Labeling.) In addition, the Panel recommends the following specific labeling: *Warnings.* (i) "Do not exceed recommended dosage except under the advice and supervision of a physician".

(ii) "Do not take this product if nausea, vomiting or restlessness occurs".

(iii) *"Caution:* Do not continue to take this product but seek medical assistance immediately if symptoms are not relieved within 1 hour or become worse".

(iv) "Do not take this product if you are presently taking a drug or suppository containing any form of theophylline except under the advice and supervision of a physician".

(v) "Do not give this product to children under 12 years except under the advice and supervision of a physician. Excessive use may cause toxic effects and even death in children".

(vi) *Professional labeling.* The Panel recommends that labeling provided to health professionals (but not to the general public) may contain the following additional dosage information: Children 2 to under 12 years oral dosage based on the anhydrous theophylline equivalent is 3.33 mg/kg of body weight 3 times daily every 8 hours not to exceed 10 mg/kg in 24 hours.

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Category I Labeling

The Panel recommends the following Category I labeling for bronchodilator active ingredients to be generally recognized as safe and effective and not misbranded as well as the specific labeling discussed in the individual ingredient statements.

a. *Indications.* (1) "For temporary relief of bronchial asthma".

(2) "For symptomatic control of bronchial asthma".

(3) "Provides temporary relief from acute symptoms of bronchial asthma".

(4) "Relaxes tense bronchial muscles to ease breathing for asthma patients".

(5) "For temporary relief of wheezing (attacks and distress) of bronchial asthma".

(6) For products to be taken by inhalation: statements as to onset of action, e.g., "fast" or "quick", must be substantiated and accompanied by a specific time, e.g., "within 5 minutes".

b. *Warnings.* (1) *"Caution:* Do not take this product unless a diagnosis of asthma has been made by a physician".

2. *Category II conditions under which bronchodilator ingredients are not generally recognized as safe and effective or are misbranded.* The use of bronchodilators under the following conditions is unsupported by scientific data, and in some instances by sound theoretical reasoning. The Panel concludes that the following ingredients and labeling should be removed from the market until scientific testing supports their use.

Category II Active Ingredients

The Panel has classified the following bronchodilator active ingredients as not generally recognized as safe and effective or as misbranded:

Belladonna alkaloids

Pseudoephedrine preparations: Pseudoephedrine hydrochloride, Pseudoephedrine sulfate

a. *Belladonna alkaloids by inhalation (as contained in Atropa belladonna and Datura stramonia).* The Panel concludes that belladonna alkaloids by inhalation are not safe and effective for OTC use in the treatment of asthma. The effectiveness of this preparation is unproven and it has great potential for drug abuse and toxicity. In view of the availability of other safer and effective OTC drugs for the treatment of asthma, the Panel concludes that there is no place for this preparation in the OTC treatment of asthma.

(1) *Safety.* A mixture of stramonium and belladonna is available and is utilized by smoking the cigarettes or pipe mixture or by burning the powder, like incense, and inhaling the smoke. Per unit dose (cigarette, pipeful, etc.), the alkaloid content presumably absorbed systemically is about 0.0125 mg (Refs. 1 and 2). However, the preparation is easily abused for its psychomimetic properties, by excessive use or ingestion of cigarettes, liquid suspensions or capsules filled with the powder (Ref. 2). Intoxication is generally characterized by confusion, delirium, hallucinations, and various anticholinergic effects, such as difficulty in swallowing due to dry mouth, blurred vision, photophobia, difficulty in urination, and constipation. Some deaths have been reported (Ref. 2). The adverse effects of excessive use of the powder have been well described (Ref. 3). There are numerous reports of intoxication us-

ing the powder or ingesting seeds or leaves of stramonium plants (Refs. 4 through 9). Clearly, products containing belladonna alkaloids present a risk to the consumer.

(2) *Effectiveness.* Belladonna alkaloids may be of benefit when given in the form of cigarettes (Ref. 9), but there has been no critical assessment of effectiveness. There are no well-controlled studies or other evidence to support its effectiveness as a bronchodilator when used by inhalation in the treatment of asthma.

(3) *Evaluation.* The Panel concludes that the effectiveness of belladonna alkaloids by inhalation is unproven. In view of the high potential for abuse and toxicity and the availability of other safe and effective drugs, the Panel concludes that belladonna alkaloids by inhalation are not safe and effective for OTC use in the treatment of asthma.

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b. *Pseudoephedrine preparations (pseudoephdrine hydrochloride, pseudoephedrine sulfate).* The Panel concludes that pseudoephedrine preparations are safe but not effective for OTC use as a bronchodilator.

(1) *Safety.* In a study of cardiovascular effects of pseudoephedrine, dose response in four subjects showed that 210 to 240 mg (3.05 to 4.0 mg/kg) were required to raise diastolic blood pressure to 90 mm Hg or above (Ref. 1). However, a serious rise in blood pressure may occur if the drug is taken concurrently with monoamine oxidase (MAO) inhibitors (Refs. 2 and 3). Skin reactions both of long and short duration may be associated with taking the drug but these are rare (Refs. 4 and 5). Six of 21 patients who took 60 mg orally had mild side effects of drowsiness, nausea, insomnia, and headache (Ref. 6).

(2) *Effectiveness.* In a careful double-blind study using 210 mg pseudoephedrine hydrochloride orally in nine subjects with reversible obstruction to air flow, measurements were made of vital capacity and forced expiratory volume in 1 second (FEV_1), which is a measurement related to airway obstruction, the higher the figure the better the air flow and the less the obstruction in the air tubes (Ref. 1).

This high dose of pseudoephedrine increased FEV_1 to less than half that produced by ephedrine. The maximum mean percentage increased in FEV_1 was only 11 percent after pseudoephedrine and this is within the variation of the technique and not considered a significant change. Ephedrine was used in the same study and caused a 27 percent improvement in FEV_1. In another double-blind placebo-controlled study, 100 to 200 mg pseudoephedrine was given intravenously and was ineffective in 12 human subjects as a bronchodilator as judged by changes in forced vital capacity (FVC) and forced expired volume (FEV_1) (Ref. 7).

(3) *Evaluation.* Based on the two studies reviewed (Refs. 1 and 7), the Panel concludes that pseudoephedrine is ineffective for use as a bronchodilator and therefore cannot be generally recognized as effective in the treatment of asthma.

REFERENCES

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(2) Elis, J. et al., "Modification by Monoamine Oxidase Inhibitors of the Effect of Some Sympathomimetics on Blood Pressure," *British Medical Journal*, 2:75–78, 1967.

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(4) Brownstein, M. H., "Fixed Eruptions Due to an Ephedrine Isomer," *Archives of Dermatology*, 97:115–119, 1968.

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(6) Arbesman, C. E. and R. J. Ehrenreich, "New Drugs in the Treatment of Allergies," *New York State Journal of Medicine*, 61:219–229, 1961.

(7) Levy, D., S. Permutt and W. F. Russell, Jr., "An Evaluation of Three Drugs Alleged to Relieve Airway Obstruction in Asthmatic Patients," *Current Therapeutic Research* 3: 174–184, 1961.

Category II Labeling

All claims that state or imply a therapeutic action or safety property peculiar to the preparation that cannot be demonstrated in controlled studies are not acceptable. The Panel has previously discussed such labeling (See part II. paragraph O. above—CCABA Product Labeling Claims Not Supported by Scientific Evidence.). However, labeling that is descriptive of the product such as its taste or appearance are acceptable.

The Panel concludes that the following labeling is misleading and contains unacceptable claims for preparations used for the treatment of asthma. The Panel assumes that preparations under consideration will contain only a sympathomimetic of the bronchodilator type and/or theophylline ingredients. The Panel believes that the language expressed in the following misleading claims is excessive and claims either too much or claims effects which do not occur. For example, most asthma preparations have no effect on hay fever, the nose, the "common cold", or on congestion. The following apply regardless of whether the preparation is given by inhalation or by mouth:

a. *Unacceptable labeling because these claimed effects do not occur with bronchodilators.* (1) "Relief of hay fever".

(2) Claims for any effects "on nasal passages".

(3) Statements related to "congestion of air tubes or lungs".

(4) "Decongests swollen membranes, acts to loosen congestion, relief of general respiratory congestion".

(5) "Relief of bronchitis or 'the common cold' ".

(6) "Relief of fear, anxiety, nervous tension".

(7) "Cleans bronchial passages".

(8) "Contains anti-allergen ingredient".

(9) "Eases irritation of bronchial and nasal mucous membranes, and itchy, watery eyes".

(10) "Relief of other respiratory conditions".

(11) "Phlegm broken up and one is able to expel the phlegm with little effort".

(12) "Nagging cough is reduced to a minimum and as a result sleep is much deeper and uninterrupted".

b. *Unacceptable labeling because of the difficulty to substantiate and the implication that high use rate is evidence of the particular effectiveness of the ingredients.* "Most prescribed or recommended by doctors in medical practice".

c. *Unacceptable labeling because the claim suggests it is particularly effective.* "Proved highly effective in medical practice". The Panel notes that effectiveness must already be established to be classified as Category I.

d. *Unacceptable labeling because the claim is excessive and difficult to substantiate.* "Effective when all other available means have failed".

e. *Unacceptable labeling because excessive claims are made in emotional terms.*

(1) "Relieves gasping for air".

(2) "Free breathing restored".

(3) "Breathes a sigh of relief".

3. *Category III conditions for which the available data are insufficient to permit final classification at this time.* The Panel concludes that adequate and reliable scientific evidence is not available at this time to permit final classification of the claimed ingredient and conditions listed below. The Panel believes it is reasonable to provide 3 years for the development and review of such evidence. Marketing need not cease during this time if adequate testing is undertaken. If adequate effectiveness data are not obtained within 3 years, however, the ingredient and conditions listed in this category should no longer be marketed in over-the-counter products. Effectiveness as a bronchodilator must be demon-

strated by controlled objective studies. Subjective data alone are unacceptable because of the marked variability in the subjective awareness of the wheezing and shortness of breath associated with asthma.

Category III Active Ingredient

The Panel concludes that the available data are insufficient to permit final classification of the following claimed bronchodilator active ingredient.

The Panel concludes that there is insufficient evidence that euphorbia pilulifera is effective as a bronchodilator.

a. *Safety.* Clinical experience has confirmed that euphorbia pilulifera is safe in the dosage ranges used as a bronchodilator. In large dosage, it is said to be an irritant to the gastric mucous membrane (Ref. 1). There is some disagreement as to its effect on the skin. In one reference it is said not to irritate the skin (Ref. 1), but in others it is said to produce vesication (Refs. 2 and 3). It produces an increase in bronchial secretion, and large doses cause vomiting and diarrhea. Limited animal experiments showed no serious side effects (Ref. 4). Marketing experience of a capsule product has resulted in no serious complaints (Ref. 4).

b. *Effectiveness.* There are no well-controlled studies documenting the effectiveness of euphorbia pilulifera as a bronchodilator. The drug has been used in the treatment of asthma and bronchitis but "its value is not apparent" (Ref. 5). In Pharmacotherapeutics, 1928, (Ref. 2) it stated: "It finds some use as a bronchodilator in spasmodic asthma and in chronic bronchitis." It has been employed as a constituent of cough mixtures containing more active drugs and it has occasionally been employed in small dose in the treatment of the "common cold" and hay fever (Ref. 2). It has been marketed in a dosage of 0.715 gm in combination with aspirin and caffeine as a capsule, and many patients have claimed relief from asthma, sinusitis, bronchitis, hay fever, and rhinitis as well as good results in colds (Ref. 4). However, there is no evidence from the references that the drug has ever had any type of scientific testing.

c. *Proposed dosage.* The Panel is unable to determine a proposed dosage. Euphorbia pilulifera has been used as an elixir, fluidextract, tincture, in capsule and powder form, and as leaves to be smoked. The dosages are as follows: Elixir euphorbiae compositum (National Formulary) 4 to 46 mg followed by 92 mg twice daily for not more than a total of 3 doses daily; 8 ml fluidextractum euphorbiae (National Formulary) 1 to 3 ml; and tinctura euphorbiae (unofficial) 0.6 to 1.8 ml; powder 0.6 to 4 gm; and capsule (no dose could be determined). These dosages are recommended in the literature (Refs. 2 and 6). There are no details regarding frequency of dosage.

The Panel concludes that the pharmaceutical industry should consult with the Food and Drug Administration as to a suitable proposed dosage for testing. Otherwise, the Panel recommends that each drug manufacturer evaluate the dosage as labeled on the manufacturer's marketed product(s).

d. *Labeling.* The Panel recommends the Category I labeling for bronchodilator active ingredients. (See part V. paragraph C. below—Category I Labeling.)

e. *Evaluation.* Data to demonstrate effectiveness as a bronchodilator will be required in accordance with the guidelines set forth below for testing bronchodilator drugs. (See part V. paragraph C. below—Data Required For Evaluation.)

REFERENCES

(1) "The Dispensatory of the United States of America," 25th Ed., Edited by Osol, A. and G. E. Farrar, J. B. Lippincott Co., Philadelphia, p. 1688, 1960.

(2) Solis-Cohen, S. and T. S. Githens, "Pharmacotherapeutics, Materia Medica and Drug Action," D. Appleton and Co., New York, p. 1391, 1928.

(3) Culbreth, D. M. R., "A Manual of Materia Medica and Pharmacology," 7th Ed., Lea and Febiger, Philadelphia, p. 372, 1927.

(4) OTC Volume 040211.

(5) Hellerman, R. C. and L. W. Hazelton, "The Antispasmodic Action of Euphorbia Pilulifera," *Journal of the American Pharmaceutical Association (Scientific Edition)*, 39:142–146, 1950.

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Category III Labeling

The Panel concludes that the available data are insufficient to permit final classification of the labeling claim identified below for bronchodilators. Additional data are required to support the following bronchodilator claim: "For temporary relief of cough caused by the 'common cold' or 'bronchitis' ". The Panel concludes that the effect of bronchodilators on cough (other than due to asthma) is uncertain.

C. DATA REQUIRED FOR EVALUATION

The Panel has agreed that the protocols recommended in this document for the studies required to substantiate Category I are in keeping with the present state of the art and do not preclude the use of any advances or improved methodology in the future.

1. *Principles in the design of an experimental protocol for testing bronchodilator drugs.* a. *General principles.* The effectiveness of a bronchodilator drug is determined by its ability to reverse the airway obstruction of patients with asthma. Although clinical improvement may be reported, it is essential to have objective measurements of pulmonary function to substantiate improvement. Tests of bronchodilator drugs should be double-blind and crossover studies. Pulmonary function tests should be performed before and after the drug or placebo is given. Objective testing should be done for a sufficient time to show the duration of action of the drug. For OTC drugs a single dose should be shown to be effective. Continual taking of the drug over days or weeks to show improvement is not acceptable for OTC products. The patient needs to get quick and obvious relief from a single dose. The drugs used should be tested in the same dosage as the purchaser might be expected to take, i.e., the recommended dosage on the label.

To show effectiveness it is necessary for two studies by two different investigators to indicate that there is definite improvement in pulmonary function following single doses of the drug under test as described under Interpretation of data, below.

b. *Selection of patients.* Selection of patients for testing should be based on the diagnosis of asthma. There should be generalized airway obstruction whose severity varies greatly over short periods of time, and this should be demonstrated by pulmonary function tests improving significantly after the use of an accepted bronchodilator drug.

c. *Methods of study.* For large series of patients, the forced vital capacity, forced expiratory volume (one second), and maximal midexpiratory flow rate are the simplest and most available tests. However, measurements of flow from flow-volume curves at 50 percent and 75 percent of the vital capacity, measurements of airway resistance and specific conductance using a body plethysmograph are recommended when the complex equipment is available.

The precise number of patients to be tested cannot be stated. However, if the drug is effective, approximately 20 patients should be sufficient for satisfactory statistical analysis of data.

d. *Interpretation of data.* Ideally, the response should be interpreted according to the recognized variability in the laboratory in which the test is being performed. Where such variability is not precisely defined, improvement of 15 to 25 percent may be considered a slight reversibility; a change of 26 to 50 percent is moderate reversibility; and greater than 50 percent is marked reversibility. However, for the purposes of an experimental protocol, statistical analysis and significance is essential.

Evidence of drug effectiveness is required from a minimum of two positive studies based on the results of two different investigators or laboratories.

All data submitted to the Food and Drug Administration must present both favorable and any unfavorable results.

e. *Evaluation of safety.* Tests of safety should involve the usual tests for toxicity to the respiratory system and be relevant to the known possible adverse effects of the drugs under testing. Tests should be done in the form of dose response curves up to maximum therapeutic effectiveness.

REFERENCE

(1) Woolf, C. R., R. Kory and J. Ross, "Criteria for the Assessment of Reversibility in Airway Obstruction," *Chest*, 65:552–553, 1974.

VI. ANTICHOLINERGICS

A. GENERAL DISCUSSION

Anticholinergics are drugs used in the symptomatic relief of excessive secretions of the nose (rhinorrhea) and eyes commonly associated with hay fever, allergy, rhinitis and the "common cold." The tissues responsible for these secretions, the glands of the nasal mucosa and

the lacrimal glands, are supplied by nerves known as cholinergic or parasympathetic nerves. These nerves release a neurohumoral substance, acetylcholine (ACh), which acts on receptors in these tissues apparently causing the excessive secretions. The anticholinergic drugs, by competing with ACh for these receptors, reduce or prevent the secretions.

There are other tissues having receptors acted on by ACh, and the anticholinergic drugs are able to prevent the response usually caused by ACh at these sites as well. These other tissues are the sweat, salivary and bronchial glands, the muscles for visual accommodation (adaptation of the eye for distinct vision at different distances), the heart, the gastrointestinal tract, and the urinary bladder. The cholinergic nerves which innervate these tissues are compositely known as the parasympathetic nervous system. All these tissues are not equally sensitive to the anticholinergic agents and the responses are dose related. Small doses depress salivary bronchial and sweat secretions. Larger doses are required to inhibit visual accommodation or increase the heart rate. Still larger doses are required to inhibit the parasympathetic control of the gastrointestinal tract or the urinary bladder.

The naturally occurring anticholinergic drugs, the alkaloids of the belladonna plants, are widely distributed in nature especially among the Solanaceae. The active drugs derived from these plants are atropine (dl-hyoscyamine) and scopolamine (l-hyoscine) depending upon which plant is the source. The official preparations of belladonna act chiefly by virtue of their atropine content.

Atropine is the classical representative of this group of anticholinergic drugs. It is dl-hyoscyamine, the stereoisomers being present in equal amounts but the activity residing in the l-form. The drying effect on the respiratory tract may be useful in the symptomatic relief of excessive secretions of the nose (rhinorrhea) and eyes commonly associated with hay fever, allergy, rhinitis and the "common cold." The effect of atropine is most noticeable if there are excessive secretions. There is no evidence that the course of the illness is altered by these drugs. At higher doses, the bronchi and bronchioles (large and small airways) are relaxed. This relaxation is most pronounced if the bronchi and bronchioles are contracted by histamine or increased parasympathetic activity and the atropine is administered by inhalation.

These drugs reduce the volume of secretions as well as making them less fluid. The less fluid secretions are more difficult to remove from the respiratory passages and may lead to obstruction. This predisposes the patient to infection. In a person with bronchial asthma or chronic obstructive pulmonary disease, this may be extremely hazardous.

The belladonna alkaloids will have little effect on the intraocular pressure of the normal eye. However, in the glaucomatous eye, when the intraocular pressure is initially above normal, they are likely to increase the intraocular pressure and damage the eye, especially in narrow angle glaucoma.

The toxic or side effects of the anticholinergic drugs are an extension of the pharmacologic effects of the drugs. These effects are dry mouth, anhydrosis, tachycardia, dilatation of the pupil and blurred vision, photophobia, restlessness, confusion and difficulty in urination. Very large doses may cause elevated body temperature and respiratory depression. Elderly men with enlargement of the prostate gland may develop urinary obstruction with less than toxic doses. There are numerous synthetic anticholinergic compounds, none of which differ significantly in pharmacologic effects or toxic effects from the naturally occurring drugs. Antihistaminics in varying degrees also have an anticholinergic effect. Antihistamines are discussed in another section of this document. (See part VII. below—Antihistamines.) Given together with an anticholinergic in the same preparation or at the same time, an antihistaminic drug will have at least an additive anticholinergic effect. With this in mind, the dose of each should be adjusted accordingly.

REFERENCES

(1) Innes, I. R. and M. Nickerson, "Drugs Inhibiting the Action of Acetylcholine on Structures Innervated by Postganglionic Parasympathetic Nerves (Antimuscarinic or Atropinic Drugs)," *in* "The Pharmacological Basis of Therapeutics," 4th Ed., Edited by Goodman, L. A. and A. Gilman, MacMillan Co., New York, pp. 524–548, 1970.

(2) "Drill's Pharmacology in Medicine," 4th Ed., Edited by DiPalma, J. R., McGraw-Hill, pp. 608–626, 1971.

B. CATEGORIZATION OF DATA

1. *Category I conditions under which anticholinergic ingredients are generally recognized as safe and effective and are not misbranded.*

Category I Active Ingredients

The Panel was unable to classify a claimed anticholinergic active ingredient as generally recognized as safe and effective and not misbranded.

Category I Labeling

The Panel recommends the following Category I labeling for anticholinergic active ingredients to be generally recognized as safe and effective and not misbranded:

a. *Indications.* (1) "For temporary relief of watery nasal discharge and watering eyes as may occur in certain allergic conditions and infections of the upper respiratory tract".

(2) "Temporarily suppresses watery nasal discharge".

(3) "Temporary relief from excessive nasal secretions".

(4) "Temporary relief from running nose".

(5) "Temporarily suppresses watering of eyes".

b. *Warnings.* (1) "Do not exceed recommended dosage except under the advice and supervision of a physician".

(2) "Do not continue to take this product if constipation, excessive dryness of the mouth, insomnia, excitement, confusion, rapid pulse, or blurring of vision occur".

(3) "*Caution:* Do not take this product if you have asthma, glaucoma or have difficulty in urination due to enlargement of the prostate gland except under the advice and supervision of a physician".

(4) "Do not give this product to children under 12 years except under the advice and supervision of a physician".

2. *Category II conditions under which anticholinergic ingredients are not generally recognized as safe and effective or are misbranded.* The use of anticholinergics under the following conditions is unsupported by scientific data, and in some instances by sound theoretical reasoning. The Panel concludes that the following ingredients and labeling should be removed from the market until scientific testing supports their use.

Category II Active Ingredients

The Panel has classified the following anticholinergic active ingredient as not generally recognized as safe and effective or as misbranded:

The Panel concludes that belladonna alkaloids (as contained in Atropa belladonna and Datura stramonia) when used by inhalation are not safe and effective for OTC use in asthma. The effectiveness of this preparation is unproven and it has great potential for drug abuse and toxicity. In view of the availability of other, safer, effective OTC drugs for the treatment of asthma, the Panel concludes that there is no place for this preparation in the OTC treatment of asthma.

a. *Safety.* The Panel has discussed the safety of belladonna alkaloids by inhalation in reference to the treatment of asthma with bronchodilators. (See part V. paragraph B.2.a. above—Belladonna alkaloids by inhalation (as contained in Atropa belladonna and Datura stramonia).)

b. *Effectiveness.* The Panel has discussed the effectiveness of belladonna alkaloids by inhalation in reference to the treatment of asthma with bronchodilators. (See part V. paragraph B.2.a. above—Belladonna alkaloids by inhalation (as contained in Atropa belladonna and Datura stramonia).)

c. *Evaluation.* The Panel concludes that the effectiveness of belladonna alkaloids by inhalation is unproven. In view of the high potential for abuse and toxicity and the availability of other drugs, the Panel concludes that belladonna alkaloids by inhalation are not safe and effective for OTC use as an anticholinergic.

Category II Labeling

The Panel concludes that the use of certain labeling claims related to the safety and/or effectiveness of the product are unsupported by scientific data, and in some instances by sound theoretical reasoning. The Panel has previously discussed such labeling. (See part II. paragraph O. above—CCABA Product Labeling Claims Not Supported by Scientific Evidence.) However, labeling that is descriptive of the product such as its taste or appearance is acceptable.

The Panel concludes that the following claims are misleading and are unacceptable for preparations used as anticholinergics:

a. *Claims not supported by scientific data.* "Clears nasal passages, open airways".

b. *All claims which state or imply a therapeutic action or safety property peculiar to the preparation that cannot be demonstrated in controlled studies.* These include claims such as "specially formulated", "scientifically improved or selected", "natural", "extra strength", "teamed components", "superior to ordinary", also claims implying a physiological effect which either has no foundation or meaning or will be meaningless or misleading to the public such as "antiallergic", "gets at the roots of", "fights", "wakes up", "recommended by doctors", and "travels through the blood stream".

c. *Claims for relief where time is indeterminate, and not supported by scientific data.* These include claims such as "all day", "all night", "for hours", "fast", and "prompt".

3. *Category III conditions for which the available data are insufficient to permit final classification at this time.* The Panel concludes that adequate and reliable scientific evidence is not available at this time to permit final classification of the claimed ingredients and conditions listed below. The Panel believes it reasonable to provide 3 years for the development and review of such evidence. Marketing need not cease during this time if adequate testing is undertaken. If adequate effectiveness data are not obtained within 3 years, however, the ingredients listed in this category should no longer be marketed as over-the-counter products. Effectiveness as an anticholinergic must be demonstrated by the ability to reduce rhinorrhea in patients with acute or chronic rhinitis. The evaluation must be a subjective study since the Panel is unaware of any technique for objective measurements.

Category III Active Ingredients

The Panel concludes that the available data are insufficient to permit final classification of the following claimed anticholinergic active ingredients: Atropine sulfate, Belladonna alkaloids.

a. *Atropine sulfate.* The Panel concludes that atropine sulfate is probably safe in the dosage range currently used (0.2 mg to 0.3 mg) as an anticholinergic but there are insufficient data to permit final classification of its effectiveness for OTC use as an anticholinergic. Although atropine at a higher dose, 0.6 mg, may be effective in relieving excessive secretions of the nose, there is no evidence that smaller doses as used in OTC preparations will do this. However, the Panel recommends that atropine not be made available for OTC use at a 0.6 mg dosage until suitable studies have been completed to show safety.

(1) *Safety.* Clinical experience has confirmed that atropine sulfate is probably safe in adults when taken orally as an anticholinergic in the currently marketed OTC dose of 0.03 mg to 0.2 mg total belladonna alkaloids. Dryness of the mouth appears first at about 0.5 mg (Ref. 1). No adverse effect was found in patients with open angle glaucoma taking 0.6 mg 3 times daily for 7 days (Ref. 2). Suppression of salivation occurred in children at the following oral doses: 1 to 12 months, 0.016 mg/kg; 12 to 36 months 0.014 mg/kg; 3 to 6 years, 0.022 mg/kg; and 6 to 12 years, 0.02 mg/kg (Ref. 3). A 7-week infant took more than 40 mg in 24 hours and recovered (Ref. 4). Ingestion of 450 mg in an adult has been followed by recovery (Ref. 5). There is a lack of data to support the use of anticholinergic active ingredients in children under the age of 12. The Pediatric Consultant Panel recommended that no dosage be marketed for children until further studies were completed. (See part II. paragraph H. above—Pediatric dosage.)

(2) *Effectiveness.* There are no well-controlled studies documenting the effectiveness of atropine sulfate as an anticholinergic. In the treatment of excessive secretions of the nose associated with the "common cold," atropine appears to be ineffective, but only one study is available (Ref. 6). The study indicated that a dose of 0.6 mg given early may transiently reduce the nasal secretions associated with the "common cold" giving some temporary comfort. However, there is no evidence that the very small doses of belladonna alkaloids per dosage unit in currently marketed OTC preparations, i.e., 0.03 to 0.2 mg total alkaloids, are effective.

(3) *Proposed dosage.* The Panel is unable to determine a proposed dosage. Although 0.6 mg atropine sulfate may be effective, the Panel concludes that such a dosage should not be available for OTC use until studies demonstrate safety. The Panel concludes that the pharmaceutical industry should consult with the Food and Drug Administration as to a suitable proposed dosage. Otherwise, the Panel recommends that each drug manufacturer evaluate the dosage as labeled on the manufacturer's marketed product. In such a case, the Panel concludes that for children under 12 years, there be no recommended dosage except under the advice and supervision of a physician.

(4) *Labeling.* The Panel recommends the Category I labeling for anticholinergic active ingredients. (See part IV. paragraph B.1. above—Category I Labeling.)

(5) *Evaluation.* Data to demonstrate effectiveness will be required in accordance with the guidelines set forth below for testing anticholinergic drugs. (See part VI. paragraph C. below—Data Required for Evaluation.)

REFERENCES

(1) Gowdy, J. M., "Stramonium Intoxication," *Journal of the American Medical Association*, 221:585–587, 1972.

(2) Lazenby, G. W., J. W. Reed and W. M. Grant, "Anticholinergic Medication in Open-Angle Glaucoma," *Archives of Ophthalmology*, 84:719–723, 1970.

(3) Unna, K. R., K. Glaser, E. Lipton and P. R. Patterson, "Dosage of Drugs in Infants and Children: I. Atropine," *Pediatrics*, 6:197–207, 1950.

(4) Joos, H. A., "Atropine Intoxication in Infancy," *American Journal of Diseases of Children*, 79:855–861, 1950.

(5) Comroe, B. I., "Atropine Poisoning: Recovery After 7½ Grains of Atropine Sulfate by Mouth," *Journal of the American Medical Association*, 101:446–447, 1933.

(6) Personnel of the U.S. Naval Medical Research Unit No. 4, "The Prophylaxis and Treatment of Acute Respiratory Diseases with Antihistaminic Drugs," *Journal of Laboratory and Clinical Medicine*, 36:555–569, 1951.

b. *Belladonna alkaloids.* The Panel concludes that the belladonna alkaloids are probably safe in the dosage range used as anticholinergics but there are insufficient data to permit final classification of their effectiveness for OTC use as anticholinergics.

(1) *Safety.* Clinical experience has confirmed that belladonna alkaloids are safe in the dosage ranges used as anticholinerics. The belladonna alkaloids contain atropine (d, dl hyoscyamine) and scopolamine (l-hyoscine) and are present in official preparations, e.g., belladonna tincture United States Pharmacopoeia (USP) and belladonna extract National Formulary (NF). These preparations act by virtue of their atropine content. Scopolamine is approximately 10 percent of the total alkaloid content and has the same pharmacological effect and toxicity as atropine, but is slightly more potent. The Panel has discussed the safety of atropine elsewhere in this document. (See part VI. paragraph B.3.a. above—Atropine sulfate.)

(2) *Effectiveness.* There are no well-controlled studies documenting the effectiveness of belladonna alkaloids as anticholinergics. Atropine and other belladonna alkaloids and substitutes reduce secretion in both the upper and the lower respiratory tract, and they are common constituents of proprietary "cold" tablets (Ref. 1). This effect in the nasopharynx may provide some symptomatic relief of acute rhinitis associated with conditions such as coryza or hay fever. However, there are no controlled studies to support this hypothesis.

The belladonna alkaloids can induce bronchial dilatation. This is particularly marked when they are administered by inhalation, but it is still less than can be achieved by other types of medication.

All antimuscarinic agents reduce the volume of bronchial secretion which results in decreased fluidity and inspissation of the residual secretion. This viscid material is difficult to remove from the respiratory tree, and its presence can dangerously obstruct airflow and predispose to infection. Because of the effect on bronchial secretion, repeated administration of any antimuscarinic to a patient with chronic lung disease must be considered as potentially hazardous.

(3) *Proposed dosage.* Adult oral dosage is 0.2 mg 2 times daily. For children under 12 years, there is no recommended dosage except under the advice and supervision of a physician.

(4) *Labeling.* The Panel recommends the Category I labeling for anticholinergic active ingredients. (See part VI. paragraph B.1. above—Category I Labeling.)

(5) *Evaluation.* Data to demonstrate effectiveness will be required in accordance with the guidelines set forth below for anticholinergic drugs. (See part VI. paragraph C. below—Data Required for Evaluation.)

REFERENCE

(1) Innes, I. R. and M. Nickerson, "Drugs Inhibiting the Action of Acetylcholine on Structures Innervated by Postganglionic Parasympathetic Nerves (Antimuscarinic or Atropinic Drugs)," *in* "The Pharmacological Basis of Therapeutics," 4th Ed., Edited by Goodman, L. S. and A. Gilman, The MacMillan Co., New York, p. 542, 1970.

Category III Labeling

The Panel concludes that the available data are insufficient to permit final classification of the labeling claim identified below for anticholinergics. Additional data are required to support the following anticholinergic claim: a. "Prolongs relief by helping to prevent further swelling and irritation."

b. The Panel concludes that claims relating to duration of action, e.g. "all day", "all night", "for hours", will require documentation.

c. *Claims that sleep will be facilitated.* These include claims such as "helps you fall asleep" and "for restful sleep".

C. DATA REQUIRED FOR EVALUATION

The Panel has agreed that the protocols recommended in this document for the studies required to bring a Category III drug into Category I are in keeping with the present state of the art and do not preclude the use of any advances or improved methodology in the future.

1. *Principles in the design of an experimental protocol for testing anticholinergic drugs.* a. *General principles.* The effectiveness of an anticholinergic drug should be determined by the ability to reduce rhinorrhea (excessive watery nasal secretions) in patients with acute or chronic rhinitis. Tests should involve double-blind placebo controlled assessment of the ability of the drug to decrease watery nasal secretions and/or tearing when administered orally and increase the comfort of the patient. This evaluation must be a subjective one since there is no technique for objective measurements. The dosage, intervals of administration and conditions for the trials should be identical to the labeled recommendations.

b. *Selection of patients.* Selection of patients for treatment should be based on the diagnosis of rhinitis with rhinorrhea. Patients with chronic allergic or vasomotor rhinitis may present more stable symptoms but in most patients rhinorrhea is a variable and inconstant symptom. Because of this, a large number of suitable patients, e.g., approximately 50 subjects depending upon the protocol, must be used and assigned in a random fashion to placebo or drug groups. Further, these groups should be matched by age and sex, and if possible, by severity of symptom. It is also highly desirable to control conditions of temperature and humidity.

c. *Methods of study.* There is nothing in the literature concerning techniques for testing rhinorrhea and it is possible that a subjective method could be developed. It might be possible to semiquantitate the degree of rhinorrhea by weighing tissues or handkerchiefs; the wet weight minus the dry weight would be a rough index of the amount of secretions per unit of time. The subjects should be evaluated on the basis of the severity of the rhinorrhea and the subject's appraisal of his discomfort. Numerical values should be assigned indicating increasing severity. A double-blind technique is used for patients with acute rhinitis and in chronic rhinitis with rhinorrhea a double-blind crossover design. Observation should be carried out for 3 to 5 days to determine the extent of possible side effects.

d. *Interpretation of data.* The data should be subjected to statistical analysis and a p value of 0.05 or less would be acceptable as evidence of drug action.

Evidence of drug effectiveness is required from a minimum of three positive studies based on the results of three different investigators or laboratories.

All data submitted to the Food and Drug Administration must present both favorable and any unfavorable results.

e. *Evaluation of safety.* Tests of safety should involve the usual tests for toxicity relevant to the known possible adverse effects of the drugs under testing. Tests should be done in the form of dose-response curves up to maximum therapeutic effectiveness.

VII. ANTIHISTAMINES

A. GENERAL DISCUSSION

1. *Development.* The antihistamines were developed in France from a series of compounds with pronounced antihistaminic activity in the laboratory but which were too toxic for clinical use. One of these antihistaminic drugs, Antergan, was used for the first time clinically in 1942 in France. This was promptly followed by pyrilamine maleate. There then followed in 1946 the appearance in the United States of diphenhydramine and tripelennamine (Ref. 1). Many active antihistamine drugs appeared soon thereafter and the total number currently marketed is probably now close to fifty.

REFERENCE

(1) Loew, E. R., "Pharmacology of Antihistamine Compounds," *Physiological Reviews*, 27:542–573, 1947.

2. *Mechanism of action.* The antihistamines are useful primarily for the symptomatic relief of certain allergic disorders (Refs. 2 through 5). They suppress symptoms presumably caused by the release of histamine and possibly other chemical mediators from mast cells in mucous membranes (Refs. 1, 2, 5, and 6). Histamine attaches to specific receptor sites at the surface of cells in the nose, eyes, lungs, and skin and causes characteristic "allergic" symptoms. The antihistamines appear to act by competing with histamine for the receptor sites. If the antihistamine reaches the receptor site first, histamine is blocked from initiating a response. In this manner, antihistamines effectively block most smooth muscle responses to histamine.

The antihistaminic drugs are well tolerated by laboratory animals and produce recognizable effects on blood pressure, heart rate or respiration when given in large oral doses. These effects are more pronounced if the drugs are given intravenously (Refs. 2 and 5).

In man, the involvement of renal (kidney), hepatic (liver), hematologic (blood) or other major body systems in adverse reactions appears to be remarkably uncommon (Refs. 5 and 7).

In the skin of man, antihistamines inhibit the wheal, flare and itch reaction that occurs within a few minutes after the injection of histamine intracutaneously (into the skin). The antihistaminic drugs also inhibit similar reactions mediated by antibodies belonging to the IgE class of immunoglobulins (antibodies), but to a somewhat lesser degree. The Panel has previously discussed the role of antibodies in allergy earlier in this document. (See part II. paragraph B.1. above—Allergy.) Examples of reactions mediated by antibodies of the IgE class are those produced by skin testing with pollen extracts in which histamine release is involved. In addition to histamine, there are other chemical mediators released in IgE mediated reactions, and the antihistaminic drugs antagonize these much less effectively if at all. It is probably for this reason that these drugs are more active in protecting against the effects of injected histamine than in protecting against anaphylaxis in animals or allergic symptoms in man.

REFERENCES

(1) Loew, E. R., "Pharmacology of Antihistamine Compounds," *Physiological Reviews*, 27:542–573, 1947.

(2) Douglas, W. W., "Histamine and Antihistamines; 5-Hydroxytryptamine and Antagonists," *in* "The Pharmacological Basis of Therapeutics," 4th Ed., Edited by Goodman, L. S. and A. Gilman, The MacMillan Co., New York, pp. 635–642, 1970.

(3) "AMA Drug Evaluations," 2d Ed., Publishing Sciences Group, Incorporated, Action, Massachusetts, pp. 491–492, 1973.

(4) "Antihistamine Drugs," *in* "American Hospital Formulary Service," The American Society of Hospital Pharmacists, Washington, D.C., 4:00, 1975.

(5) Beckman, H., "Pharmacology; The Nature, Action and Use of Drugs," 2d Ed., The W. B. Saunders Co., Philadelphia, 1961.

(6) Roth, F. E. and I. I. A. Tabachnick, "Histamine and Antihistamines," *in* "Drill's Pharmacology in Medicine," 4th Ed., Edited by Dipalma, McGraw Hill Co., New York, pp. 995–1020, 1971.

(7) Wyngaarden, J. B. and M. H. Seevers, "The Toxic Effects of Antihistamine Drugs," *Journal of the American Medical Association*, 145:277–282, 1951.

3. *Preclinical studies.* As a group the antihistamines have the capacity to decrease or suppress effects produced by histamine in animals (Refs. 1 through 4). Animal "models" are therefore useful in determining drugs which will have antihistamine activity. An animal commonly used is the guinea pig. Guinea pigs can be protected by an antihistaminic drug from the often fatal narrowing of the air passages in the lung (bronchoconstriction) produced by histamine which causes death by asphyxia. Likewise, contraction of isolated tissues

of the guinea pig intestine (ileum) and of the airways of the trachea and bronchus produced by histamine is prevented by antihistamines in in vitro studies. These effects are most easily demonstrated in the guinea pig because of the animal's intense sensitivity to histamine but the antihistaminic drugs also act in a similar manner in some other laboratory animals and in man (Refs. 1 through 3).

The antihistaminic drugs are somewhat protective in experimental allergic reactions (anaphylaxis) but their action here is not so intense as their action against histamine. Apparently in man, some allergic reactions (hay fever and hives) are caused entirely or in large part by histamine release whereas other reactions, for example asthma, are not. The capacity to block the symptom-producing effects of histamine presumably explains why antihistamines are effective in relieving the symptoms of hay fever and hives (consisting of rashes associated with itching wheals) in which release of histamine appears to be the main cause of the symptoms (Refs. 2 and 3).

In concentrations that are effective against the spasmogenic activity of histamine, antihistamines have little or no capacity to counter the spasmogenic activity of other drugs such as acetylcholine, nicotine or barium.

Gastric ulcers with perforation have occurred in guinea pigs receiving both histamine and antihistamine under highly artificial conditions (Ref. 3). The experiment depends on the fact that antihistamine drugs can protect against histamine-induced bronchospasm and asphyxia although the antihistaminic drugs do not prevent another action of histamine which is to stimulate the production of acid within the stomach. Under the conditions of the experiment, increased acid production is induced in the guinea pig by giving large doses of histamine. The antihistamine protects the guinea pig from bronchospasm and fatal asphyxia which the histamine would otherwise cause. The Panel finds, therefore, that the antihistaminic drugs play no ulcer-producing role in this type of experiment and there are no other data which would implicate the antihistaminic drugs in promoting acid production in the stomach or ulcer.

In view of the chemical heterogeneity of the antihistamines, there is a surprising unanimity among the statements of critical investigators and authorities in describing their antihistaminic actions. The antihistamines under consideration are described as being intense antagonists of histamine, are of low acute (Ref. 1) and chronic (Ref. 2) toxicity and most are effective in suppressing the symptoms of allergic rhinitis (Refs. 1, 2, 3, 5, and 6). It is because these attributes are shared by most or all of the antihistamine drugs that individual drugs are not often singled out for special attention in the texts reviewed.

REFERENCES

(1) Roth, F. E. and I. I. A. Tabachnick, "Histamine and Antihistamines," *in* "Drill's Pharmacology in Medicine," 4th Ed., Edited by Dipalma, J., McGraw-Hill Co., New York, pp. 995–1020, 1971.

(2) Beckman, H., "Pharmacology; The Nature, Action and Use of Drugs," 2d Ed., The W. B. Saunders Co., Philadelphia, 1961.

(3) Douglas, W. W., "Histamine and Antihistamines; 5-Hydroxytryptamine and Antagonists," *in* "The Pharmacological Basis of Therapeutics," 4th Ed., Edited by Goodman, L. S. and A. Gilman, The MacMillan Co., New York, pp. 635–642, 1970.

(4) Loew, E. R., "Pharmacology of Antihistamine Compounds," *Physiological Reviews*, 27:542–573, 1947.

(5) "AMA Drug Evaluations," 2d Ed., Publishing Sciences Group, Incorporated, Acton, Massachusetts, pp. 491–492, 1973.

(6) "Antihistamine Drugs," *in* "American Hospital Formulary Service," The American Society of Hospital Pharmacists, Washington, D.C., 4:00, 1975.

4. *Common side effects.* Among the antihistamines, there are minor differences in the nature and frequency of side effects and toxicity which are related to chemical class (Refs. 1 through 3). With the exception of phenindamine, all the antihistamines considered by the Panel cause central nervous system depression, often recognized as drowsiness (sedation). Drowsiness is most marked among the antihistamines from the chemical class known as the ethanolamines, e.g., diphenhydramine, doxylamine and phenyltoloxamine, and least marked among the alkylamines, e.g., chlorpheniramine, brompheniramine and pheniramine. The ethylenediamines, e.g., methapyrilene, pyrilamine maleate, thenyldiamine and thonzylamine, are intermediate in this respect.

There is a wide range of susceptibility to actions of the antihistaminic drugs especially as regards the central nervous system. The chief danger from overdosage of antihistamines is central nervous system depression. The ethanolamines, (e.g., diphenhydramine and doxylamine) and the ethylenediamines, (e.g., methapyrilene) are also used as mild sleep inducers, and the ethanolamines, (e.g., diphenhydramine and dimenhydrinate) and the ethylenediamines, (e.g., methazine) as antiemetics for the treatment of the symptoms of motion sickness. Some are useful in treating paralysis agitans and petit mal seizures. No exact explanation for these actions is available.

Stimulation of the central nervous system has been observed in patients with focal cortical lesions in whom small doses of antihistamines may cause electroencephalographic activity and even frank seizures (Ref. 4). However, the precise basis for this stimulation is not fully understood. Excessive doses in any patient may cause restlessness, excitation, delirium, tremors, and even convulsions (Refs. 1 through 3). Phenindamine causes stimulation rather than depression as a common side effect and is unique in this respect among the antihistamines under consideration. The Panel has discussed this side effect observed with phenindamine later in this document. (See part VII. paragraph B.1.f. below—Phenindamine tartrate.)

Dryness of the mouth is also a common side effect of the antihistaminic drugs. Other side effects which are not as common as drowsiness have been reported in scientific texts but are poorly documented and often cannot be definitely ascribed to antihistamines. These include gastrointestinal effects such as anorexia (appetite loss), nausea, vomiting, epigastric distress, constipation or diarrhea (Ref. 1).

Also reported are cardiovascular symptoms which may include palpitations, hypotension, headache or tightness of the chest (Ref. 1). In the genitourinary system, an effect on the frequency of urination and/or dysuria may be encountered (Ref. 1). Cutaneous side effects such as urticarial, eczematous, bullous, or petechial rashes and photosensitivity may occur (Ref. 5). Hematologic complications that have been reported have included rare occurrences of pancytopenia, thrombocytopenia, hemolytic anemia and agranulocytosis (Ref. 5).

The Panel concludes that serious side effects produced by the antihistaminic drugs in the dosages recommended for OTC use are rare and the more common side effects are rarely serious.

REFERENCES

(1) Douglas, W. W., "Histamine and Antihistamine; 5-Hydroxytryptamine and Antagonists," *in* "The Pharmacological Basis of Therapeutics," 4th Ed., Edited by Goodman, L. S. and A. Gilman, The MacMillan Co., New York, pp. 635–642, 1970.

(2) Beckman, H. "Pharmacology; The Nature, Action and Use of Drugs," 2d Ed., The W. B. Saunders Co., Philadelphia, 1961.

(3) Roth, F. E. and I. I. A. Tabachnick, "Histamine and Antihistamines," *in* "Drill's Pharmacology in Medicine," 4th Ed., Edited by Dipalma, J., McGraw-Hill Co., New York, pp. 995–1020, 1971.

(4) King, G. and S. D. Weeks, "Pyribenzamine Activation of the Encephalogram, EEG," *Clinical Neurophysiology*, 18:503, 1965.

(5) "AMA Drug Evaluations," 2d Ed., Publishing Sciences Group, Incorporated, Acton, Massachusetts, pp. 491–492, 1973.

5. *Reduction of nasal secretions.* A common but variable action of the antihistaminic drugs is their anticholinergic effect of reducing nasal secretions. Some patients describe this as a disagreeable drying effect. In the recommended dosage, the drying effect of most antihistamines is less intense than that of atropine. This action appears to be entirely palliative and does not alter or shorten the course of the illness. The Panel is aware that a controversy exists concerning the use of antihistamines in patients with bronchial asthma where a "drying action" is undesirable. Many physicians consider this effect to be disadvantageous in patients with bronchial asthma and some maintain that the antihistaminic drugs are contraindicated in patients with this disease.

It is the view of the Panel that in the presence of allergic rhinitis and in the "common cold," secretions are often excessive and a "drying" agent may then be appropriate. However, the Panel finds, as do other investigators, that effectiveness of antihistamines widely used in the "common cold" has not been demonstrated in controlled studies (Ref. 1). In

addition, the Panel concludes that there is no evidence that release of histamine is either the cause of symptoms in the "common cold" nor is histamine release a significant factor in the "common cold." This will be discussed more fully below. (See part VII. paragraph C.2. below—Principles in the design of an experimental protocol for testing antihistamine drugs in the "common cold.")

REFERENCE

(1) West, S., B. Brandon, P. Stolley and R. Rumrill, "A Review of Antihistamines and the Common Cold," *Pediatrics*, 56:100–107, 1975.

6. *Human toxicity.* Unlike other classes of drugs, the extensive clinical experience with antihistamines has fairly well identified virtually all of the central nervous system manifestations of toxicity. The Panel has extensively reviewed these known toxic symptoms. While many of the more severe symptoms of antihistamines are relatively rare or are due to large doses or accidental overdose, the Panel has included them in the interest of completeness of this review.

Although rare, fatal or near fatal doses cause fixed, dilated pupils; muscular twitching followed by convulsions, sometimes with opisthotonos; coma; circulatory collapse; and respiratory failure. Convulsions may persist for 24 hours, coma for several days. Death rarely occurs later than 24 hours after ingestion unless due to infection associated with agranulocytosis (Ref. 1).

Because of the unique nature and wide use of antihistaminic drugs and because of the lack of extensive well-controlled clinical studies, the Panel has reviewed adverse reaction reporting systems to obtain a better understanding of the safety of antihistamines. Two major sources of data are the adverse reaction files of the Food and Drug Administration and the latest Poison Control Studies of the National Clearinghouse for Poison Control Centers. Since antihistamines have been extensively marketed for nearly 30 years, the Panel believes that a review of adverse reactions reports will serve as an indication of their safety.

It should be emphasized that these information sources are not entirely accurate nor do they necessarily give a valid picture of the incidence or prevalence of particular side effects. However, these reporting mechanisms do highlight the types of adverse reactions that can be expected. Where massive overdoses are ingested, such as in suicide attempts, these reports give a clearer picture of an ingredient's toxicological profile, significant elements of which include morbidity levels, toxic reactions which occur at varying dosage levels as well as dosage levels at which reversibility of an ingredient's toxic effects may occur.

The latest "Poison Control Statistics," published by the National Clearinghouse for Poison Control Centers provides the latest published data now available and covers the period from January to December, 1973 (Ref. 2). This publication presents collective toxicity data on household products and medicines from the Nation's 580 Poison Control Centers. This information reflects the treatment or response to each telephone inquiry to the Poison Control Centers concerning a poisoning or accidental ingestion and usually is not verified for accuracy except for the more obvious incongruities. Although only 1973 statistics were reviewed in detail by the Panel, that particular year is considered representative of all the years for which this type data was compiled.

Unlike the Poison Control Center data the adverse reaction data compiled by the Food and Drug Administration are cumulative and represent the total number of reported cases since the reporting system was implemented in 1968. Adverse reactions are reported to the agency in a variety of ways and at various levels of sophistication. These sources include hospitals, physicians, pharmaceutical manufacturers, consumers, or Food and Drug Administration personnel who often obtained these reports from consumers and physicians. While some of the data are verified for accuracy, they are often incomplete. Data are reported as having one of four causal relationships: directly related, probably related, possibly related and remotely related. For the Panel's purposes, only the adverse reactions which are directly or probably related to drug ingestion are discussed. The Panel recognizes that the statistics generated by the Poison Control Center and the Food and Drug Administration can be misleading and must be carefully used in determining the potential health threat of ingredients to consumers because the extenuating circumstances of each individual case are not represented.

A review of these two sources reveals several variables in the collection and comprehensiveness of the data which must be taken into consideration for a realistic view of the statistics compiled. For example, in the Poison Control Center data, few of the ingestions were of a single chemical entity. Most ingestions were of multi-ingredient products identified by brand name or conversly were ingestion of multiple products. Thus, it is improper to clearly attribute the symptom(s) reported to any one ingredient contained in a product. Further, in some cases no clear delineation of the quantity or number of units of an agent ingested is given. These data were often incomplete and left blank or "unknown" on the document. Of those listing a quantity, several were found to be at normal or subnormal dosage levels with no symptoms exhibited. These cases are included in the Poison Control Statistics as a reported "poisoning" when in fact no "poisoning" occurred. In addition, reported cases of hospitalization allude to symptoms serious enough to require treatment in a hospital, but give no indication whether the patient was seen only at the emergency room or actually admitted for treatment. Many of these same weaknesses and inconsistencies in data collection and assimilation also appear in the compilations from the Food and Drug Administration.

The Panel concludes that summaries of the Poison Control Statistics and the data from the Food and Drug Administration can only be used as an indication of the potential threat posed by OTC products because ingestions of both prescription and OTC products are combined in such statistics.

REFERENCES

(1) Loew, E. R., "Pharmacology of Benadryl and the Specificity of Antihistamine Drugs," *Annals of the New York Academy of Sciences*, 50:1142, 1950.

(2) "Poison Control Statistics, 1973," National Clearinghouse for Poison Control Centers, Bethesda, 1973.

7. *Criteria for classification of antihistamines as Category I.* In evaluating the antihistamines submitted for review, the Panel established the following criteria for classification of an ingredient as safe and effective and not misbranded for use as an antihistamine:

a. *Antihistamine activity.* If an ingredient has been tested in animal models and demonstrated to have antihistamine activity, i.e., in vitro test and in vivo tests (animal challenge with histamine and animal anaphylaxis protection), the findings were used to support a Category I determination.

b. *Animal toxicity.* If an ingredient has been tested in animals and found to have a low order of toxicity, the findings were used to support a Category I determination.

c. *Clinical studies.* If an ingredient has been tested clinically and the studies were determined to be controlled double-blind studies of an adequate design that included an appropriate dosing interval for each age group of patients, the findings were used to support a Category I determination. The Panel has discussed adequate design for clinical testing later in this document. (See part VII. paragraph C. below—Data Required for Evaluation.)

d. *Clinical experience.* If an ingredient has been subjected to uncontrolled clinical trials and has been shown to have sufficiently broad acceptable clinical use, i.e., general use and recognition by the medical community of safety and effectiveness for the treatment of allergic rhinitis, the findings were used to support a Category I determination. The Panel has determined that such clinical use may have been acquired while the ingredient was marketed and available only by prescription but only when used for the treatment of allergic rhinitis similar to that to be encountered with OTC use.

e. *Acceptable side effects.* If an ingredient is shown to have side effects in man for which appropriate labeling can be established, i.e., adequate directions for use and warnings against unsafe use such as "May cause drowsiness", the findings were used to support a Category I determination. In considering the acceptability of these side effects, the Panel questioned whether warnings were sufficient or whether the degree of side effects, and possibility of abuse or misuse under ordinary conditions of use, could be compensated for with adequate labeling. The Panel finds that this is an

especially important consideration for recommended dosages of ingredients higher than those currently available for OTC use, e.g., chlorpheniramine 4 mg or for ingredients previously not available for OTC use, e.g., diphenhydramine.

The Panel has summarized the findings in the following table:

Active ingredients	Antihistamine activity [1]	Animal toxicity [2]	Clinical studies [3]	Clinical experience [4]	Acceptable side effects [5]
Brompheniramine maleate	+	+	+	+	+
Chlorpheniramine Maleate	+	+	+	+	+
Diphenhydramine hydrochloride	+	+	0	+	++
Doxylamine succinate	+	+	+	+	++
Methapyrilene fumarate and hydrochloride.	+	+	0	+	++
Phenindamine tartrate	+	+	0	+	+−
Pheniramine maleate	+	+	0	+	++
Phenyltoloxamine citrate	+	+	0	0	+
Promethazine hydrochloride	+	+	0	+	++
Pyrilamine maleate	+	+	0	+	+
Thenyldiamine hydrochloride	+	+	0	0	0
Thonzylamine hydrochloride	+	+	0	+	+

[1] The (+) symbol indicates that the ingredient showed antihistamine activity in animals.
[2] The (+) symbol indicates that animal studies are available and show low toxicity.
[3] The (+) symbol indicates that controlled double-blind clinical studies of adequate design are available. The (0) symbol indicates that no data are available.
[4] The (+) symbol indicates that adequate clinical experience with the ingredient exists. The (0) symbol indicates that no data are available.
[5] The (+) symbol indicates a positive finding of "drowsiness." The (++) symbol indicates a positive finding of "marked drowsiness." The (+−) symbol indicates a positive finding of either "drowsiness" or "nervousness and insomnia." The (0) symbol indicates that no data are available.

The Panel has determined that if four of the five criteria are satisfied (antihistamine activity, animal toxicity, clinical experience and acceptable side effects), the ingredient may be classified as Category I. The Panel has further determined that the availability of clinical studies is not always required for each ingredient. The Panel has fully discussed these ingredients in the appropriate sections below. (See part VII. paragraph B. below—Categorization of Data.)

6. *Summary.* The antihistamine ingredients as a group are strikingly antihistaminic in animal models. This is their main pharmacologic action and appears to be closely related to their clinical effectiveness. The Panel has found that three of these ingredients, chlorpheniramine, brompheniramine, and doxylamine, have been subjected to controlled clinical studies which support their clinical effectiveness. For most of the remaining ingredients marketed OTC, extensive clinical use over a period exceeding 20 years indicates that these antihistaminic drugs are also effective in treating allergic rhinitis. As a group the antihistamines possess a low order of toxicity which the Panel feels is essential for the use of any ingredient in the OTC market.

B. CATEGORIZATION OF DATA

1. *Category I conditions under which antihistamine ingredients are generally recognized as safe and effective and are not misbranded.*

Category I Active Ingredients

The Panel has classified the following antihistamine active ingredients as generally recognized as safe and effective and not misbranded:

Brompheniramine maleate
Chlorpheniramine maleate
Diphenhydramine hydrochloride
Doxylamine succinate
Methapyrilene preparations: Methapyrilene fumarate, Methapyrilene hydrochloride
Phenindamine tartrate
Pheniramine maleate
Promethazine hydrochloride
Pyrilamine maleate
Thonzylamine hydrochloride

a. *Brompheniramine maleate.* The Panel concludes that brompheniramine maleate is safe and effective for OTC use as an antihistamine in suppressing the symptoms of allergic rhinitis as specified in the dosage section discussed below.

(1) *Safety.* Studies in animals indicate that brompheniramine maleate has low toxicity (Ref. 1). The chief side effect of brompheniramine is sedation which occurs in about 20 percent or less of patients taking clinically effective doses (Refs. 2 and 3). Also observed is an atropine-like effect (anticholinergic action), which is not pronounced, but might have an adverse effect in patients with narrow angle glaucoma. The drying effect due to atropine-like action has been considered to be disadvantageous in patients with asthma because drying of secretions interferes with their removal from the airway. However, the Panel is unable to find evidence that these possible adverse effects are of clinical significance (Ref. 4).

Recovery from accidental overdosage with brompheniramine indicates that this drug has a wide margin of safety (Ref. 5). An injection of 100 mg caused only dry mouth 8 hours later in a hospitalized patient (Ref. 5). Observations in children indicate a relatively low degree of toxicity for brompheniramine (Ref. 2).

A 6-year-old boy tolerated 8 mg/lb/24 hours orally. A 2-year-old boy received a single oral dose of 60 mg without side effects and a 4-year-old boy received 96 mg in a single dose and subsequently had mild drowsiness. A 2½-year-old boy ingested an estimated twenty-five 12 mg tablets in whom hyperactivity and convulsions occurred followed by gastric lavage 2½ hours later with final recovery (Refs. 1 and 6).

The Panel is aware of a reported case of agranulocytosis following therapy with two antihistaminic drugs, thenalidine tartrate and parabromdylamine maleate (Ref. 7). The incident occurred during 1958 in which a 64-year-old female had taken both drugs. The drug manufacturer of thenalidine tartrate discontinued marketing the ingredient within months of its reported association in the medical literature with agranulocytosis. The other drug, parabromdylamine maleate, is also known as brompheniramine maleate. The patient had taken 4 mg brompheniramine maleate orally 4 times daily concurrently with an antibiotic ointment for the treatment of a pruritic rash. The patient received a total dose of 568 mg brompheniramine maleate over a period of approximately 60 days. The symptoms persisted and the drug was discontinued at which time 25 mg thenalidine tartrate was given orally 4 times daily for an additional period of approximately 60 days for a total dose of 1,850 mg thenalidine maleate prior to hospitalization. The author reporting the case noted that previous investigators had reported three cases of agranulocytosis associated with thenalidine tartrate therapy (Ref. 8). The Panel concludes that the data do not adequately substantiate that brompheniramine maleate was the causative factor in producing the blood dyscrasia. The drug has been extensively marketed and available by prescription for over 15 years with no documented cases of agranulocytosis occurring.

The Panel has considered the most recent data available from the records compiled from Poison Control Centers during 1973 in which a minimum of 600 million dosage units of brompheniramine maleate were sold. (See part VII. paragraph A.6. above—Human toxicity.) Of the 568 reported cases of suspected poisonings for brompheniramine maleate, 17.1 percent exhibited some symptoms and 5.5 percent exhibited symptoms serious enough to require treatment or observation at a hospital. There was one fatality reported with the drug identified as a contributing cause of death but it was not possible to determine whether the ingestion was accidental or suicidal.

The Panel's review of the data supplied by the Food and Drug Administration showed a total of 47 adverse reaction reports on three marketed products containing brompheniramine since 1968 (Ref. 9). Of the 47, no adverse reactions were listed as being definitely related to ingestion of brompheniramine, 43 were listed as probably caused by ingestion of the drug and 4 were listed as possibly related to its ingestion.

The only other serious adverse reaction, aplastic anemia, was listed as possibly related to brompheniramine ingestion. A review of the source document disclosed few details of the case except that several other drugs were also ingested. The Panel was unable to conclude from the sketchy data whether there was any relationship between ingestion of brompheniramine and the aplastic anemia.

It should be noted that while brompheniramine is currently available only by prescription, the dosage levels are comparable to those that would be available in OTC use. Therefore, the safety considerations presented to the Panel for prescription marketing have given a reasonably accurate picture of what to expect from OTC use of this ingredient.

The Panel concludes that brompheniramine maleate is safe for OTC use as an antihistamine in the dosage ranges described below.

(2) *Effectiveness.* Studies in animals have shown brompheniramine to have intense antihistaminic activity and to protect against anaphylaxis (Refs. 1 and 6). In addition to its demonstrated effectiveness as an antihistamine and protection against anaphylaxis in animals, brompheniramine has been shown in double-blind studies in humans to be effective in suppressing the symptoms of allergic rhinitis in doses of 4 mg or more given at 4 to 6 hour intervals (Refs. 10 through 12).

Available evidence indicates that brompheniramine has about the same effectiveness on a mg for mg basis as chlorpheniramine (Ref. 13).

In studies of the treatment of perennial rhinitis, efficacy was reported in 23 children ages 2 months to 2 years at a dosage of 0.2 mg to 0.5 mg/lb in 24 hours divided into 3 doses (Ref. 2). Likewise, 0.2 mg/lb in 24 hours was reported as effective in 28 children ages 2 to 6 years and 0.15 mg/lb in 24 hours in 16 children ages 6 to 14 years. Most of these patients had received other antihistamines without benefit. In addition to treatment with brompheniramine, all had been instructed in environmental control measures and many were receiving injections of allergenic extracts. The contribution made by these measures to the reported benefit cannot be assessed. There were no controlled groups although the statement is made that the patients were selected by "alternate allocation," the meaning of which is unclear. The statement that over three-fourths of the patients had failed to obtain benefit from "various other antihistaminic agents" is surprising in the light of what is known today about the efficacy of the antihistaminic drugs in rhinitis. Therefore, the Panel concludes that evidence of effectiveness for children is insufficient.

The Panel concludes that brompheniramine maleate 4 mg is the minimum effective OTC dosage for the relief of the symptoms of allergic rhinitis.

(3) *Dosage.* Adult oral dosage is 4 mg every 4 to 6 hours not to exceed 24 mg in 24 hours. Children 6 to under 12 years oral dosage is 2 mg every 4 to 6 hours not to exceed 12 mg in 24 hours. Children 2 to under 6 years oral dosage is identified in the labeling section discussed below under professional labeling. For children under 2 years, there is no recommended dosage except under the advice and supervision of a physician.

(4) *Labeling.* The Panel recommends the Category I labeling for antihistamine active ingredients. (See part VII. paragraph B.1. below—Catagory I Labeling.) In addition, the Panel recommends the following specific labeling: *Professional labeling.* The Panel recommends that labeling provided to health professionals (but not to the general public) may contain the following additional dosage information: Children 2 to under 6 years oral dosage is 1 mg every 4 to 6 hours not to exceed 6 mg in 24 hours.

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b. *Chlorpheniramine maleate.* The Panel concludes that chlorpheniramine maleate is safe and effective for OTC use as an antihistamine in suppressing the symptoms of allergic rhinitis as specified in the dosage section discussed below.

(1) *Safety.* The chief side effect of chlorpheniramine is sedation which occurs in about 10 to 20 percent of persons taking clinically effective doses. The drug also has a mild atropine-like effect (anticholinergic action) in some patients. This effect might have an adverse effect in patients with narrow angle glaucoma. Likewise, a drying effect has been considered to be a disadvantage in patients with asthma because drying of secretions interferes with their removal from the airways. Data supporting these potentially adverse effects in glaucoma and asthma are not available. Overdosage with chlorpheniramine has been relatively well tolerated. Adults receiving 1.5 gm orally in 69 hours and 200 mg in a single intramuscular dose recovered from the induced side effects without incident (Ref. 1) as did a 4-year-old boy who received 175 mg orally in 3½ hours (Ref. 2).

The Panel has considered the most recent data available from the records compiled from Poison Control Centers during 1973 in which a minimum of 2 billion dosage units of chlorpheniramine maleate were sold. (See part VII. paragraph A.6. above—Human toxicity.) Of the 1,609 reported suspected poisonings for chlorpheniramine maleate 15.8 percent exhibited some symptoms and 5.3 percent exhibited symptoms serious enough to require treatment or observation at a hospital. There were no fatalities reported with the drug.

The Panel's review of the data supplied by the Food and Drug Administration disclosed a total of 14 adverse reaction reports on chlorpheniramine since 1968 (Ref. 3). Of the 14 reports, no adverse reactions were listed as being definitely related to ingestion of chlorpheniramine, three were listed as probably caused by this drug's ingestion, five were listed as possibly related to its ingestion and six were listed as remotely related to ingestion of this drug.

It should be noted that chlorpheniramine is available by prescription at the 4 mg dosage level and OTC at the 2 mg dosage level. However, the safety picture presented by the prescription dosage level has given the Panel a reasonably accurate idea of what to expect from OTC marketing of the 4 mg dosage level.

The Panel concludes that chlorpheniramine maleate is safe for OTC use as an antihistamine in the dosage ranges described below.

(2) *Effectiveness.* Chlorpheniramine has been demonstrated to be effective in animal challenge tests with histamine in anaphylaxis protection (Ref. 4). In addition, its effectiveness in doses of 4 to 8 mg 4 times daily in the treatment of allergic rhinitis is described in a number of articles and uncontrolled studies and is supported by controlled studies (Refs. 5 through 8).

In a double-blind controlled study of the effectiveness of doxylamine succinate, chlorpheniramine was included as a standard of effectiveness. In this study 7.5 mg and 12.5 mg doxylamine were compared with chlorpheniramine 4 mg and a placebo, all given 4 times daily. Each group contained approximately 40 patients and the study extended for 1½ days. Chlorpheniramine and both dosages of doxylamine gave relief of pollen-induced symptoms of allergic rhinitis as compared with the placebo. The effectiveness of chlorpheniramine 4 mg was not significantly different from 7.5 or 12.5 mg doxylamine. In this study measurements of resistance to nasal air flow were made and failed to show any effect of the antihistamine preparations as compared with the placebo (Ref. 9). Other studies corroborate this finding. Using measurements of resistance to airflow in the nose, a well-controlled study

to determine the effect of chlorpheniramine given in an oral dose of 4 mg on relief of nasal obstruction gave no objective evidence of any effect over a period of 4 hours (Ref. 10). There was a significant decrease in resistance to flow when pseudoephedrine was given in a dose of 30 mg, indicating that the method was capable of revealing therapeutic effect. Likewise, a study submitted in an OTC Volume showed increased nasal obstruction in patients with nonallergic acute rhinitis after 8 mg chlorpheniramine in sustained action form (Ref. 11). Both of these studies were done in patients without evidence of allergy. These studies indicate that chlorpheniramine does not relieve and indeed, may aggravate nasal obstruction.

Only one study (Ref. 5) appears to have been done using a 2 mg dose, which is commonly used in OTC preparations, demonstrating effectiveness. The Panel concludes that chlorpheniramine maleate has not been shown to be effective for adults at a dose less than 4 mg.

The Panel concludes that chlorpheniramine maleate 4 mg is the minimum effective OTC dosage for adults for the relief of the symptoms of allergic rhinitis.

(3) *Dosage.* Adult oral dosage is 4 mg every 4 to 6 hours not to exceed 24 mg in 24 hours. Children 6 to under 12 years oral dosage is 2 mg every 4 to 6 hours not to exceed 12 mg in 24 hours. Children 2 to under 6 years oral dosage is identified in the labeling section discussed below under professional labeling. For children under 2 years, there is no recommended dosage except under the advice and supervision of a physician.

(4) *Labeling.* The Panel recommends the Category I labeling for antihistamine active ingredients. (See part VII. paragraph B.1. below—Category I Labeling.) In addition the Panel recommends the following specific labeling: *Professional labeling.* The Panel recommends that labeling provided to health professionals (but not to the general public) may contain the following additional dosage information: Children 2 to under 6 years oral dosage is 1 mg every 4 to 6 hours not to exceed 6 mg in 24 hours.

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c. *Diphenhydramine hydrochloride.* The Panel concludes that diphenhydramine hydrochloride is safe and effective for OTC use as an antihistamine in suppressing the symptoms of allergic rhinitis as specified in the dosage section discussed below.

(1) *Safety.* Diphenhydramine has a low order of toxicity in laboratory animals (Ref. 1). Its first clinical use was in 1946. Since then it has been used widely for treatment of such common conditions as allergic rhinitis, sundry rashes, the "common cold", and has also been used as a sedative. With the exception of sedation, adverse effects have been rare and the drug is considered safe. The Panel has also reviewed the side effects and toxicity of diphenhydramine when used as an antitussive and finds it to be safe when used at the same dosage level and regimen. That safety discussion is included elsewhere in this document. See part III. paragraph B.1.c. above—Diphenhydramine hydrochloride.)

In a double-blind study in 20 males (Ref. 2) there was no evidence of interference with tests for memory, rotary pursuit, or reaction time at a dose of 12.5 mg or 25 mg. These doses are below that recommended for adults on the treatment of allergic rhinitis. Clinical experience indicates that about 50 percent of persons have drowsiness as a side effect when 50 mg is given (Refs. 3 and 4). In some individuals, this occurs to a degree which would probably impair competence in driving a car or operating machinery. An atropine-like effect is also frequently described by patients as a drying sensation of the mouth and nose.

Many toxicologic studies have been carried out on diphenhydramine hydrochloride. Unpublished animal studies performed with mice demonstrated the LD_{50} to be 145 mg/kg and 263.0 mg/kg (Refs. 5 through 7). In rats, the LD_{50} was found to be 520 mg/kg and 549.5 mg/kg. The results of these studies are very similar when different animal strains, times when the studies were run, and variations inherent under different laboratory conditions are considered (Ref. 5). Diphenhydramine hydrochloride was demonstrated to have low toxicity in all three studies. Based upon these studies the usual adult human oral dosage level of 50 mg or 0.7 mg/kg 3 to 4 times daily is $\frac{1}{200}$th of the oral LD_{50} of diphenhydramine hydrochloride in mice (the LD_{50} is equivalent to at least 200 times the therapeutic dose in man) and $\frac{1}{100}$th the LD_{50} in rats (the LD_{50} is equivalent to at least 700 times the therapeutic dose in man) (Ref. 5).

In chronic toxicity studies dogs were given diphenhydramine hydrochloride at dosage levels of 10, 25, 40 and 60 mg/kg/day for periods up to 6 months. There were no gross microscopic pathologic changes attributable to diphenhydramine hydrochloride (Ref. 5).

Toxic psychoses from overdoses of diphenhydramine have occurred. A case of schizophrenic-like behavior was described by Nigro (Ref. 8). Possibly the earliest suicide was that reported by Duerfeldt in 1947 (Ref. 9).

Wyngaarden and Seevers also found that very high doses of diphenhydramine in infants may cause excitement and convulsions. They reviewed three cases in children under 3 years of age ($2\frac{1}{2}$, $1\frac{2}{3}$, and $1\frac{1}{2}$ years of age) who had taken 850 mg, 800 mg and 150 to 250 mg of diphenhydramine respectively with all doses resulting in convulsions (Ref. 10). In another case, a 32-month-old baby swallowed 9 capsules (450 mg) of diphenhydramine, after which a state of excitation was observed. Phenobarbital was prescribed, and the next day, the baby was normal (Ref. 10).

They also reviewed a group of adults ranging from 18 to 72 years, who sustained nonfatal convulsions, excitation, toxic psychosis, coma, petit mal, or somnolence (Ref. 10).

One case involved a 72-year-old asthmatic man, weighing 145 pounds who ingested 2,500 mg (50 capsules) of diphenhydramine hydrochloride. He fell into a deep sleep. Approximately 16 hours later, he awoke, feeling well. He had received no medication for this somnolence. In other cases dealing with adult fatalities, Wyngaarden and Seevers found that the ability to withstand large overdoses appears to increase with age, and the older the patient, the more the toxic manifestation shifts from that of central nervous system stimulation to that of depression. But it was also seen that a 47-year-old severely asthmatic woman died in depression after ingesting only 200 mg of diphenhydramine hydrochloride. However, the death cannot be unequivocally attributed to diphenhydramine since the shock-like state observed could well have been a complication of the disease itself and could easily have been influenced by other depressant medicaments that were given (Ref. 9).

The Panel considered the most recent data available from the records compiled from Poison Control Centers during 1973 in which a minimum of 187.4 million dosage units of diphenhydramine hydrochloride were sold. (See part VII. paragraph A.6. above—Human toxicity.) Of the 334 reported suspected poisonings for diphenhydramine hydrochloride, 37.4 percent exhibited some symptoms and 16.5 percent exhibited symptoms serious enough to require treatment or observation at a hospital. There were two fatalities reported with the drug identified as a contributing cause of death.

The Panel's review of the data supplied by the Food and Drug Administration disclosed a total of 178 adverse reaction reports on diphenhydramine since 1968 (Ref. 11). Of those 178 reports, nine were listed as definitely related to diphenhydramine ingestion, 95 were listed as probably caused by the drug's ingestion, 58 were listed as possibly related to its ingestion and 16 were listed as remotely related to diphenhydramine ingestion.

A 69-year-old female who had a history of serious medical problems and

drug ingestion was diagnosed to have agranulocytosis. Three days after termination of pentazocine lactate by injection and 1 day after termination of diphenhydramine therapy, her white blood cell count progressively climbed to normal values (Ref. 11).

The Panel is aware that recently there was some concern expressed about the potential for misuse and abuse of diphenhydramine. This concern was contained in the statement of the Commissioner of Food and Drugs, which was included in the preamble to the report of the OTC Advisory Panel on Sedatives, Tranquilizers and Sleep Aid Drug Products and published in the FEDERAL REGISTER of December 8, 1975 (40 FR 57292). This Panel will not attempt to comment on the findings of the other Panel or on the societal impact or abuse potential of diphenhydramine when used as an OTC nighttime sleep-aid. However, after a review of all the available data, the Panel concluded that diphenhydramine, as well as the other antihistamines reviewed, have a very low abuse potential and that there is little if any evidence of tolerance or habituation. However, the Panel does recognize that doses of diphenhydramine higher than those recommended for OTC use are likely to result in some side effects but that these side effects are sufficient to discourage abuse or misuse. In addition, the two pharmacologic groups for which this Panel is recommending diphenhydramine for OTC use, i.e., as an antitussive and as an antihistamine, are not recognized as being abusable by the drug abusing subculture. It should also be noted that diphenhydramine is available without a prescription for use as an antihistamine in Canada, the United Kingdom, and many other industrialized countries of the world. The Panel was unable to determine that significant abuse of this ingredient was a problem in any of these countries.

The Panel notes that the dosage levels of diphenhydramine currently available by prescription are comparable to those that would be available for OTC use. Therefore, the safety considerations presented to the Panel for prescription marketing have given a reasonably accurate picture of what to expect from OTC use of this ingredient.

The Panel concludes that diphenhydramine hydrochloride is safe for OTC use as an antihistamine in the dosage ranges described below.

(2) *Effectiveness.* In animal tests, diphenhydramine has an intense antihistamine action both in vitro (Refs. 1 and 12) and in vivo (Refs. 1 and 13). The drug gives protection to guinea pigs against anaphylactic shock (Ref. 13).

Diphenhydramine is also effective for the symptomatic treatment of allergic rhinitis. Although no studies with a double-blind control were found, the Panel's opinion concerning effectiveness in the treatment of allergic rhinitis rests on wide usage over a period of 30 years.

A number of uncontrolled clinical studies indicate that the drug is effective in relieving the symptoms of allergic rhinitis (Refs. 14 through 16) and one study also describes reduction of whealing in the skin induced by intracutaneous injection of both histamine and allergic extracts in patients with hay fever (Ref. 17). The Panel has also found the drug to be effective for use as an antitussive, which is discussed elsewhere in this document. (See part III. paragraph B.1.c. above—Diphenhydramine hydrochloride.)

The Panel concludes that diphenhydramine hydrochloride 25 to 50 mg is an effective OTC dosage range for the relief of the symptoms of allergic rhinitis.

(3) *Dosage.* Adult oral dosage is 25 to 50 mg every 4 to 6 hours not to exceed 300 mg in 24 hours. Children 6 to under 12 years oral dosage is 12.5 to 25 mg every 4 to 6 hours not to exceed 150 mg in 24 hours. Children 2 to under 6 years oral dosage is identified in the labeling section discussed below under professional labeling. For children under 2 years, there is no recommended dosage except under the advice and supervision of a physician.

(4) *Labeling.* The Panel recommends the Category I labeling for antihistaminic active ingredients. (See part VII. paragraph B.1. below—Category I Labeling.) In addition, the Panel recommends the following specific labeling: (i) *Warning.* "May cause marked drowsiness."

(ii) *Professional labeling.* The Panel recommends that labeling provided to health professionals (but not to the general public) may contain the following additional dosage information: Children 2 to under 6 years oral dosage is 6.25 to 12.5 mg every 4 to 6 hours not to exceed 75 mg in 24 hours.

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d. *Doxylamine Succinate.* The Panel concludes that doxylamine succinate is safe and effective for OTC use as an antihistamine in suppressing the symptoms of allergic rhinitis as specified in the dosage section discussed below.

(1) *Safety.* Doxylamine has a low oral toxicity in laboratory animals (LD_{50}: mice 470 mg/kg; rabbits 250 mg/kg) at doses which greatly exceed those required to demonstrate antihistaminic effects (Ref. 1). Brown and Werner found the intravenous LD_{50} to be 49 and 62 mg/kg for rabbits and mice, respectively (Ref. 1). The subcutaneous dose in mice was about 87 percent less toxic than when given intravenously. The oral dose was about 80 percent less toxic than when given in rabbits. The administration of doses of doxylamine succinate as high as 45 mg/kg twice daily for a period of 38 days had no significant effect in rats. Repeated administration of increasing doses from 50 to 150 mg/kg also had no gross effects. However, an increase to 200 mg/kg resulted in a decreased rate of growth in some animals, and an increase up to 400 mg/kg caused lack of appetite and death in one case. Thus, repeated doses resulted in toxicity only when the doses approached acutely lethal ones (Ref. 1). Daily administration of doxylamine to dogs, rats and monkeys in doses of 3 to 7.5 mg/kg for 2 months gave no evidence of accumulation and the drug was well tolerated (Ref. 2).

Clinical experience indicates that the primary side effect in humans is central nervous system depression. Standard scientific tests state that there is a high incidence of sedation at the usual therapeutic dosage of 12.5 to 25 mg up to 4 times daily (Refs. 3 through 7). In one double-blind, placebo controlled study, the hypnotic effectiveness of doxylamine, 25 to 50 mg, was greater than that of 100 mg secobarbital (Ref. 8). Dizziness and nervousness occur less frequently than sedation (Ref. 3).

One study reports that of 118 patients being treated for allergy with doses of

12.5 to 50 mg of doxylamine succinate, side effects were observed in 39 (Ref. 9). Sedation or sleepiness was seen in 36 of these 39 patients or 92 percent. Nervousness was noted in four patients, and vertigo in four others. No serious toxic effects were noted after use of the drug for 6 months. Sheldon et al. (Ref. 10) gave allergic patients 12.5 to 50 mg of doxylamine succinate and found that 57 percent complained of drowsiness. However, there was no apparent correlation, they stated, between the dosage of the drug and drowsiness. Palpitation, irritability, and diarrhea were noted in three patients. There was no evidence of any hepatic, renal or vascular changes. In the study by Ferguson there was no change in pulse, respiration, temperature or blood pressure with high doses of up to 1,600 mg of doxylamine succinate daily by mouth for up to 6 months (Ref. 11). Blood chemistry and organ function tests remained normal. In addition, Ferguson found that there has been no habituation to doxylamine, but he noted a mild degree of tolerance (Ref. 11).

Selzer and Waldman gave chronic psychotic patients doses of doxylamine (unspecified salt) up to 900 mg/day for 3 months in which side effects were virtually nonexistent (Ref. 12).

In a review of antihistaminic drugs, it is reported that 36 percent of 56 patients receiving the drug for treatment of allergic rhinitis had side effects, chiefly drowsiness (Ref. 13).

It appears from some studies that 50 mg and above of doxylamine succinate produces the side effect of sedation which is characteristic of antihistamines (Refs. 9 and 13). However, as stated above, Ferguson (Ref. 11) and Selzer and Waldman (Ref. 12) gave doses up to 900 mg daily in three divided doses with little evidence of drowsiness in the schizophrenic patients. Such apparently contradictory results have not yet been explained.

The Panel has considered the most recent data available from the records compiled from Poison Control Centers during 1973 in which a minimum of 60 million dosage units of doxylamine succinate were sold. (See part VII. paragraph A.6. above—Human toxicity.) Of the 100 suspected poisonings reported for doxylamine succinate, 32 percent exhibited some symptoms and 5 percent exhibited symptoms serious enough to require treatment or observation at a hospital. There were no fatalities reported with the drug.

The Panel has reviewed and concurs with the statement in the report of the Advisory Review Panel on OTC Sedatives, Tranquilizers and Sleep-Aid Drug Products published in the FEDERAL REGISTER of December 8, 1975 (40 FR 57292) "that no literature was found by the Panel concerning poisoning or doses which cause death in humans."

The Panel's review of the data supplied by the Food and Drug Administration disclosed a total of 10 adverse reaction reports on doxylamine succinate since 1968 (Ref. 14). Of the 10 reports none was listed as directly related to ingestion of doxylamine succinate, five were listed as probably caused by this drug's ingestion, three were listed as possibly related to its ingestion and two were listed as remotely related to ingestion of doxylamine succinate.

The Panel concludes that doxylamine succinate is safe for OTC use as an antihistamine in the dosage ranges described below.

(2) *Effectiveness.* Doxylamine is highly active in the protection of guinea pigs against the intravenous injection of histamine (Ref. 1). Using ileum strips in vitro, marked antihistaminic action was also demonstrated. The drug was also effective in protecting guinea pigs against anaphylaxis (Ref. 1).

Clinical experience and standard scientific textbooks indicate that doxylamine is an effective antihistamine in dosages of 12.5 to 25 mg up to 4 times daily (Refs. 3, 7, and 15).

Two double-blind clinical trials have demonstrated the effectiveness of doxylamine in a dosage of 12.5 and 25 mg up to 4 times daily in the treatment of hay fever (Refs. 15 and 16). In these studies, subjective evaluations by patients and physicians were logged and analyzed.

In a third well-designed study, doxylamine was given in a dose of 7.5 mg to one group and in a dose of 12.5 mg to a second group and a placebo to a third group, all with allergic rhinitis caused by pollen. The preparations were administered 4 times a day as required for 6 days with double-blind control. There were 40 to 45 patients in each group. Both the 7.5 mg and 12.5 mg dosages gave significant relief of symptoms as compared with the placebo, with the effectiveness of 12.5 mg exceeding that of 7.5 mg (Ref. 17). The incidence of drowsiness in both the 7.5 mg and 12.5 mg groups was not different from placebo.

In a fourth well-designed study with double-blind control, 7.5 and 12.5 mg doxylamine were compared with chlorpheniramine 4 mg and a placebo, all given 4 times daily. Each group contained approximately 40 patients and the study extended for 1½ days. Chlorpheniramine and both dosages of doxylamine gave relief of pollen-induced symptoms of allergic rhinitis as compared with the placebo. The effectiveness of chlorpheniramine 4 mg was not significantly different from either 7.5 or 12.5 mg doxylamine. In this study, measurements of resistance to nasal air flow were made and failed to show any effect of the antihistamine preparations as compared with the placebo (Ref. 17). One study ranked doxylamine 8th in a series of 13 antihistamines tested for antihistamine activity in man (histamine wheal test) (Ref. 18). Doxylamine has also been described as being slightly "less potent" than promethazine but having a longer duration of action (Ref. 5). An effective dosage for children 6 to 12 years of age is 6.25 mg 2 to 4 times daily (Ref. 3) or 2 mg/kg/24 hours of 60 mg/m²/24 hours divided in 4 to 6 doses (Ref. 19).

The Panel concludes that doxylamine succinate 7.5 mg is the minimum effective OTC dosage for the relief of the symptoms of allergic rhinitis.

(3) *Dosage.* Adult oral dosage is 7.5 to 12.5 mg every 4 to 6 hours not to exceed 75 mg in 24 hours. Children 6 to under 12 years oral dosage is 3.75 to 6.25 mg every 4 to 6 hours not to exceed 37.5 mg in 24 hours. Children 2 to under 6 years oral dosage is identified in the labeling section discussed below under professional labeling. For children under 2 years, there is no recommended dosage except under the advice and supervision of a physician.

(4) *Labeling.* The Panel recommends the Category I labeling for antihistamine active ingredients. (See part VII. paragraph B.1. below—Category I Labeling.) In addition, the Panel recommends the following specific labeling: (i) *Warning.* "May cause marked drowsiness."

(ii) *Professional labeling.* The Panel recommends that labeling provided to health professionals (but not to the general public) may contain the following additional dosage information: Children 2 to under 6 years oral dosage is 1.9 to 3.125 mg every 4 to 6 hours not to exceed 18.75 mg in 24 hours.

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e. *Methapyrilene preparations (methapyrilene fumarate, methapyrilene hydrochloride).* The Panel concludes that methapyrilene fumarate and methapyriline hydrochloride are safe and effective for OTC use as antihistamines in suppressing the symptoms of allergic rhinitis as specified in the dosage section discussed below.

(1) *Safety.* In animal studies, methapyrilene appears to have a low order of toxicity in laboratory animals as compared with other common antihistaminics (Refs. 1 and 2). From the results of human studies, methapyrilene appears to be safe at the recommended dosage (Ref. 3). Specifically, in the Friedlaender and Friedlaender study (Ref. 4) of 117 patients, one or more side effects, usually mild in nature, were encountered in approximately 25 percent of the patients receiving methapyrilene hydrochloride. These occurred most often when doses of 100 mg were administered but usually abated after the initial treatment and seldom affected the continued use of the drug. In most instances, a reduction in dosage to 50 mg obviated the side effects while not modifying the effectiveness. Drowsiness, the most common side effect, occurred in 13 patients. Vertigo, headache, nausea and vomiting, diarrhea and excessive dryness of mouth were next in order of frequency. No serious toxic effect was observed in any patients in this group receiving a daily dose of 200 to 300 mg (50 mg every 4 to 6 hours) (Ref. 4).

In another study, Peirce and Mothersill studied 77 patients and reported that five patients who had been treated with methapyrilene hydrochloride in daily amounts of 100 to 200 mg showed minor side effects but no toxic symptoms (Ref. 5). Rarely did side effects interfere with the patient's ability to continue the administration of the drug. In some cases, lowering the dosage obviated the side effects without significantly altering the therapeutic effectiveness of the drug. Peirce and Mothersill concluded that, ordinarily, 200 mg could be taken daily with "no discomfort" (Ref. 5).

Douglas stated that methapyrilene hydrochloride has been found to have low to intermediate activity for sedation, and its action is less pronounced than that of other antihistamines in therapeutic doses, particularly diphenhydramine (Ref. 3). Occasionally, the anticholinergic action of antihistamines generally may predominate and methapyrilene may cause excitation that results in insomnia, tremors, nervousness, irritability, and palpitation. Dryness of mouth, blurred vision, urinary retention, tachycardia, and constipation may also occur, but these reactions are rare unless large doses are used (Ref. 3). This same view of the toxicity of methapyrilene also appears in several other standard scientific texts (AMA Drug Evaluation, and New and Nonofficial Drugs) (Refs. 6 and 7). However, AMA Drug Evaluation also states that convulsions have been reported in patients with focal lesions of the cerebral cortex and in individuals who have ingested toxic doses (Refs. 6 and 7).

In a study of three patients receiving 400 mg a day for 8 to 10 weeks, no change in blood or urine constituents was observed (Ref. 4). An accidental overdose of 800 mg methapyrilene in a 20-month-old infant resulted in cyanosis, loss of consciousness, convulsions, and cardiorespiratory depression with eventual recovery (Ref. 8). An unusual case of fever, rigor, vomiting, and general malaise with recovery after 3 days is also described (Ref. 9). The symptoms recurred after challenge with methapyrilene 2 weeks after the initial attack. An 18-year-old man who became stuporous after ingestion of an unknown quantity of methapyrilene recovered (Ref. 10).

Methapyrilene fatalities have included a 16-month-old girl who developed hyperpyrexia, cerebral edema, upper nephron nephrosis and uremia (Ref. 11), an adult suicide who died in convulsions after ingestion of methapyrilene (Ref. 12), and two other adults who were found dead (Refs. 13 and 14). Nonfatal cases include two adults (Ref. 15) manifesting convulsions, and two other adults in coma (Ref. 16).

The panel has considered the most recent data available from the records compiled from Poison Control Centers during 1973 in which 543 million dosage units of methapyrilene were sold. (See part VII. paragraph A.6. above—Human toxicity.) Of the 168 suspected poisonings reported for methapyrilene fumarate or methapyrilene hydrochloride, 11.9 percent exhibited some symptoms and 5.9 percent exhibited symptoms serious enough to require treatment or observation at a hospital. There were no fatalities reported with the drug.

The Panel's review of the data supplied by the Food and Drug Administration showed a total of one adverse reaction report on methapyrilene since 1968 (Ref. 17).

The Panel concludes that methapyrilene fumerate and methapyrilene hydrochloride are safe for OTC use as antihistamines in the dosage ranges described below.

(2) *Effectiveness.* Tests in animal models have demonstrated methapyrilene's specific antihistamine activity. Methapyrilene prevents histamine-induced contraction of the guinea pig ileum and protects sensitized guinea pigs from anaphylactic shock when challenged with an antigen (Refs. 2 and 18).

No double-blind human studies using methapyrilene alone were found. Uncontrolled studies of methapyrilene reported that 63 to 79 percent of patients suffering from hives or hay fever were relieved following administration of the drug (Refs. 4, 5, 15, 18, and 19). In the Friedlaender study, approximately 75 percent of the 40 patients suffering from acute seasonal hay fever obtained some benefit from methapyrilene fumarate or methapyrilene hydrochloride, although the relief of the symptoms was seldom complete. This study utilized 100 mg doses in adults, administered 4 times daily, after meals and at bedtime (Ref. 20).

The Peirce and Mothersill study found that 75 patients received methapyrilene hydrochloride for periods varying from 1 day to 3 months (Ref. 5). The medication exhibited its greatest effectiveness in acute skin rash due to drug and food allergy, watery eyes and runny nose due to pollen sensitivity, and histamine induced headaches. They found that the effective dosage ranged from 50 to 400 mg daily. The average maintenance dose for all cases was between 150 to 200 mg daily (Ref. 5).

In the Feinberg and Bernstein study of 112 patients with allergic rhinitis (seasonal as well as that due to the pollen of trees, grasses and weeds, and to the spores of molds), 79 patients or 70 percent benefited from methapyrilene hydrochloride. Of 95 patients with vasomotor rhinitis (nonseasonal hay fever) 44 patients or 46 percent received some measure of relief (Ref. 19). The symptoms of asthma were not appreciably altered in 30 patients although the preasthmatic, spasmodic cough was decidedly helped in 6 out of 9 patients. The subjective symptoms of skin rash were helped in 4 of 12 patients. In 13 patients with atopic dermatitis (skin rash), 8 obtained considerable relief from itching. The average dose of methapyrilene hydrochloride in the Feinberg-Bernstein study was 50 mg orally, 1 to 4 times daily (Ref. 19). A controlled study of 236 patients receiving methapyrilene and 203 receiving powdered starch presented no evidence that methapyrilene aborted or ameliorated colds (Ref. 20).

The Panel concludes that methapyrilene fumarate 50 mg and methapyrilene hydrochloride 50 mg are the minimum effective OTC dosages for the relief of the symptoms of allergic rhinitis.

(3) *Dosage.* Adult oral dosage is 50 mg every 4 to 6 hours not to exceed 300 mg in 24 hours. Children 6 to under 12 years oral dosage is 25 mg every 4 to 6 hours not to exceed 150 mg in 24 hours. Children 2 to under 6 years oral dosage is identified in the labeling section discussed below under professional labeling. For children under 2 years, there is no recommended dosage except under the advice and supervision of a physician.

(4) *Labeling.* The Panel recommends the Category I labeling for antihistamine active ingredients. (See part VII. paragraph B.1. below—Category I Labeling.) In addition, the Panel recommends the following specific labeling: (i) *Warning.* "May cause marked drowsiness."

(ii) *Professional labeling.* The Panel recommends that labeling provided to health professionals, but not to the general public may contain the following additional dosage information: Children 2 to under 6 years oral dosage is 12.5 mg every 4 to 6 hours not to exceed 75 mg in 24 hours.

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f. Phenindamine tartrate. The Panel concludes that phenindamine tartrate is safe and effective for OTC use as an antihistamine in suppressing the symptoms of allergic rhinitis as specified in the dosage section discussed below.

(1) *Safety.* Acute toxicity studies in guinea pigs indicated an LD_{50} value of 125 mg intraperitoneally which is approximately the same as the intraperitoneal LD_{50} value for diphenhydramine. Daily doses of 100 mg for 5 months or of 200 mg for 6 months were reported to have no adverse effects on the weight, blood formation, blood glucose and non protein nitrogen of dogs. No histopathological changes were found (Refs. 1 and 2).

In 136 healthy subjects ingesting 75 to 600 mg phenindamine daily for 7 to 31 days, toxicity studies revealed no abnormality of hemoglobin, red cell count or white cell count, urinalysis, blood pressure, electrocardiogram, gastric acidity, glucose tolerance, pulse rate, basal metabolic rate or blood chemistry (Ref. 3). In 15 healthy volunteers receiving 50 mg or more daily for 6 months, the blood and urine remained normal (Ref. 4).

In 280 patients receiving 25 to 150 mg daily (adults averaging 75 mg; children 30 mg daily), there were side effects in 27 percent (Ref. 1). In more than 1,000 subjects side effects were frequent but mild and were directly related to dosage. At 75 mg daily, 15 percent of the subjects developed side effects. At 150 mg daily, 25 percent of 380 patients developed side effects. At 300 mg daily, 50 percent of the patients suffered side reactions, and many discontinued the drug. Receiving a dose of 600 mg daily for 7 days, 75 percent of the patients developed side effects (Refs. 3 and 5). Side effects included insomnia, stimulation, nervousness, dryness of mouth, and drowsiness (Refs. 1 through 6).

The Panel recognizes that phenindamine may produce stimulation in some persons and drowsiness in others (Ref. 7). In one study, stimulation is reported to have occurred in 35 percent of patients (Ref. 4). In a review of clinical studies (Ref. 7) comprising 250 patients with allergic rhinitis, it was reported that 3 percent had drowsiness and 12 percent had stimulation. However, data that would establish the frequency of stimulation or drowsiness among those taking the drug in recommended dosages are inadequate and cannot be used for making phenindamine an exception with respect to a warning regarding the occurrence of drowsiness as a side effect.

The Panel has considered the most recent data available from the records compiled from Poison Control Centers during 1973 in which a minimum of 14 million dosage units were sold. (See part VII. paragraph A.6. above—Human toxicity.) Of the 118 reported suspected poisonings for phenidamine tartrate, 21.2 percent exhibited some symptoms and 10.2 percent exhibited symptoms serious enough to require treatment or observation at a hospital. There were no fatalities reported with the drug.

The Panel's review of the data supplied by the Food and Drug Administration disclosed no adverse reaction reports on phenindamine tartrate since 1968 (Ref. 8).

The Panel concludes that phenindamine tartrate is safe for OTC use as an antihistamine in the dosage ranges described below.

(2) *Effectiveness.* The Panel concludes on the basis of clinical reports that phenindamine tartrate is effective for OTC use in the treatment of the symptoms of allergic rhinitis (Refs. 2, 3 and 6).

Phenindamine tartrate demonstrated antihistaminic activity in animals. It could protect guinea pigs against lethal doses of histamine. The histamine-induced contraction of guinea pig intestinal strips in vitro was inhibited by phenindamine. The drug also had a protective action in guinea pigs against fatal anaphylactic shock produced by horse serum sensitization (Refs. 1 and 2).

Clinical trials have also shown the effectiveness of phenindamine tartrate as an antihistamine in man. A dose of 200 mg of phenindamine inhibited the wheals and flares produced in ragweed-sensitive patients after they were skin-tested with ragweed or histamine (Ref. 2).

In a subjective, uncontrolled clinical evaluation of phenindamine in 389 patients with allergic conditions such as hay fever, allergic perennial rhinitis, bronchial asthma, atopic dermatitis, contact dermatitis, urticaria and angioneurotic edema, and migraine, a dose of 25 mg every 4 hours was given orally (Ref. 2). Of the 180 patients in the study with hay fever who took the drug during the hay fever season, 44 percent reported complete relief, 32 percent reported moderate relief, 14 percent had slight relief and 10 percent reported no relief. In the 71 patients with allergic perennial rhinitis, 35 percent had complete relief, 39 percent moderate relief, 9 percent slight relief and 17 percent had no relief. The relief from a dose of 25 mg lasted approximately 2 to 5 hours. Of the 389 patients, 23 percent had side reactions such as nervousness, palpitations, nausea, vomiting, insomnia, drowsiness, headache, constipation, etc. No appreciable change was seen in blood pressure or electrocardiogram.

In another report, 78.2 percent of 197 patients with hay fever who were given a daily dose of 25 to 150 mg of phenindamine for an average of 17 days reported fair to excellent relief (Ref. 1). The drug was of benefit to 76.1 percent of the 71 patients with nonseasonal vasomotor rhinitis in this study.

The symptomatic relief of allergic rhinitis by daily doses of 25 to 200 mg of phenindamine was studied in 131 patients. Seventy-five to 100 percent relief was reported by 105 of these patients whose ages ranged from 2 to 70 years. Only 27 of the patients complained of side effects (Ref. 6). In a study of 40 patients with hay fever, a daily dose of 25 to 75 mg gave marked relief to 52.5 percent, moderate relief to 25 percent, slight relief to 15 percent and 7.5 percent had no relief (Ref. 4). Daily doses of 75 to 120 mg phenindamine for 15 to 120 days to 66 hay fever subjects gave complete

relief to 18 percent, partial relief to 62 percent and 20 percent were not helped (Ref. 3). Daily doses of 75 to 250 mg to 25 patients with vasomotor rhinitis brought no relief for 44 percent and complete relief for 20 percent. At 75 mg daily, approximately 15 percent of the patients showed side effects.

Experience has also indicated that the duration of effect of one 25 mg dose is 2 to 10 hours averaging 4 to 5 hours. The onset of action is rapid, occurring within 15 minutes of ingestion (Ref. 1). In one study, 86 percent of 66 patients with hay fever received moderate to complete relief receiving a dosage of 75 to 150 mg daily. In a review of the antihistamine drugs (Ref. 7), 76 percent of 912 patients with allergic rhinitis were benefited.

In one study, moderate to marked relief of hay fever occurred in 78 percent of 40 patients taking 50 mg daily (Ref. 4).

Seventy-eight percent of patients with hay fever noted fair to excellent relief (Ref. 1). A placebo failed to provide relief of the symptoms in these patients.

The Panel concludes that phenindamine tartrate 25 mg is the minimum effective OTC dosage for the relief of the symptoms of allergic rhinitis.

(3) *Dosage.* Adult oral dosage is 25 mg every 4 to 6 hours not to exceed 150 mg in 24 hours. Children 6 to under 12 years oral dosage is 12.5 mg every 4 to 6 hours not to exceed 75 mg in 24 hours. Children 2 to under 6 years oral dosage is identified in the labeling section discussed below under professional labeling. For children under 2 years, there is no recommended dosage except under the advice and supervision of a physician.

(4) *Labeling.* The Panel recommends the Category I labeling for antihistamine active ingredients (See Part VII. paragraph B.1. below—Category I Labeling.) In addition, the Panel recommends the following specific labeling: (i) *Warning.* "*Caution:* May cause nervousness and insomnia in some individuals."

(ii) *Professional labeling.* The Panel recommends that labeling provided to health professionals (but not to the general public) may contain the following additional dosage information: Children 2 to under 6 years oral dosage is 6.25 mg every 4 to 6 hours not to exceed 37.5 mg in 24 hours.

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g. *Pheniramine maleate.* The Panel concludes that pheniramine maleate is safe and effective for OTC use as an antihistamine in suppressing the symptoms of allergic rhinitis as specified in the dosage section discussed below.

(1) *Safety.* Pheniramine maleate has been shown in animal experiments to possess a high degree of antihistaminic activity and a low order of toxicity (Refs. 1 and 2). Clinical experience has confirmed that pheniramine maleate is safe in the dosage ranges used as an antihistamine. The chief side effect of pheniramine appears to be sedation. It also appears to have a mild atropine-like effect. Since most of the studies have been done with other drugs combined with pheniramine, the action of this drug alone cannot be described with certainty. In one study in which pheniramine alone was given, drowsiness and dryness of the mouth (atropine-like effect) occurred in 11 percent of the subjects (Ref. 3). In a review of clinical studies with the antihistamine drugs (Ref. 4) 29 percent of 49 patients receiving pheniramine maleate 25 mg for allergic rhinitis had side effects; chiefly drowsiness. Among 184 subjects receiving 10 mg pheniramine 4 times daily in the course of a double-blind study of the "common cold," side effects, chiefly drowsiness, did not significantly exceed the side effects in an equal number of subjects receiving a placebo (Ref. 5). There appear to be no reports of accidental overdose. A single case was described in which acute psychosis occurred following treatment for 2 months with pheniramine 25 mg 3 times daily (Ref. 6). Following withdrawal of pheniramine, recovery occurred in 8 days. No definite conclusion could be drawn in this case as to the role played by pheniramine. An atropine-like effect suggests a potential hazard in patients with enlargement of the prostate gland and also narrow angle glaucoma and this effect has also been considered to be disadvantageous in patients with asthma although data supporting this potentially adverse effect are not available.

The Panel has considered the most recent data available from the records compiled from Poison Control Centers during 1973 in which a minimum of 291 million dosage units were sold. (See part VII. paragraph A.6. above—Human toxicity.) Of the 358 suspected poisonings reported for pheniramine maleate, 20 percent exhibited some symptoms and 1.7 percent exhibited symptoms serious enough to require treatment or observation at a hospital. There were no fatalities reported with the drug identified as a contributing cause of death.

The Panel's review of the data supplied by the Food and Drug Administration disclosed no adverse reaction reports on pheniramine maleate since 1968 (Ref. 7).

The Panel concludes that pheniramine maleate is safe for OTC use as an antihistamine in the dosage ranges described below.

(2) *Effectiveness.* Pheniramine maleate has been shown in animal experiments to possess a high degree of antihistaminic activity (Refs. 1 and 2).

There are no well-controlled studies documenting the effectiveness of pheniramine maleate as an antihistamine. In a review of several reports of clinical experience, pheniramine in a dose of 25 mg gave relief of allergic rhinitis in 81 percent of 442 patients (Ref. 4). Likewise the drug gave relief in 66 percent of patients with nonallergic rhinitis (vasomotor rhinitis).

The Panel concludes that pheniramine maleate 12.5 mg is the minimum effective OTC dosage for the relief of the symptoms of allergic rhinitis.

(3) *Dosage.* Adult oral dosage is 12.5 to 25 mg every 4 or 6 hours not to exceed 150 mg in 24 hours. Children 6 to under 12 years oral dosage is 6.25 to 12.5 mg every 4 to 6 hours not to exceed 75 mg in 24 hours. Children 2 to under 6 years oral dosage is identified in the labeling section discussed below under professional labeling. For children under 2 years, there is no recommended dosage except under the advice and supervision of a physician.

(4) *Labeling.* The Panel recommends the Category I labeling for antihistamine active ingredients (See part VII. paragraph B.1. below—Category I Labeling.) In addition, the Panel recommends the following specific labeling: (i) *Warning.* "May cause marked drowsiness".

(ii) *Professional labeling.* The Panel recommends that labeling provided to health professionals, (but not to the general public), may contain the following additional dosage information: Children 2 to under 6 years oral dosage is 3.125 to 6.25 mg every 4 to 6 hours not to exceed 37.5 mg in 24 hours.

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h. *Promethazine hydrochloride.* The Panel concludes that promethazine hydrochloride is safe and effective for OTC use as an antihistamine in suppressing the symptoms of allergic rhinitis as specified in the dosage section discussed below.

(1) *Safety.* Promethazine is well-tolerated by laboratory animals; doses which greatly exceed those giving protection against histamine are well tolerated by guinea pigs (Ref. 1). Like other antihistamine drugs, promethazine may cause drowsiness when taken in clinically effective doses. In a study in which up to 1 gm was administered therapeutically 4 times daily to psychiatric patients, drowsiness occurred as the most important and frequent side effect (Ref. 2). In a suicide attempt a 35-year-old female survived an estimated dose of 1.5 gm, developing coma and clonic contractions (Ref. 3). Another such case had a similar course after the patient consumed 500 mg of promethazine (Ref. 4). Children may be less tolerant of this drug. Seven to 10 hours after a 12-year-old boy ingested 200 mg, he was hospitalized with many symptoms including restlessness, excitation, stupor, fright and hallucinations. Recovery followed in 3 days (Ref. 5).

The Panel has considered the most recent data available from the records compiled from Poison Control Centers during 1973 in which a minimum of 385 million dosage units were sold. (See part VII. paragraph A.6. above—Human toxicity.) Of the 56 reported suspected poisonings for promethazine, 28.6 percent exhibited some symptoms and 14.3 percent exhibited symptoms serious enough to require treatment or observation at a hospital. There were no fatalities reported with the drug. This relative incidence of adverse reactions is remarkably low in light of the substantial and long use of the drug (4½ billion oral doses have been used since 1951 (Ref. 6)).

The Panel's review of the data supplied by the Food and Drug Administration showed a total of 169 adverse reactions involving marketed products containing promethazine (Ref. 7). Of the 169, 4 adverse reactions were listed as being definitely related to the oral ingestion or injection of promethazine, 105 were listed as probably caused by the drug's use, 49 were listed as possibly related to its use and 11 were listed as remotely related to promethazine.

Of particular concern are blood dyscrasias which have been reportedly associated with the drug. A total of five adverse experience reports have remotely related blood dyscrasias to promethazine. Analysis of the experience reports indicates that these dyscrasias are not attributable to promethazine. One case of agranulocytosis is reported to have occurred in a patient who was receiving promethazine and methaqualone. The patient's white blood cell count and the neutrophils began to increase and returned to normal 3 days after methaqualone was discontinued. Agranulocytosis was reported in another patient receiving large doses of two antibiotics intravenously who was also receiving oral promethazine. Additional drugs in the regimen included a thyroid derivative and tetracycline prior to the other medications. This blood dyscrasia may well be attributed to the two antibiotics, methacillin and/or cephalothin, both of which are known to cause agranulocytosis. A case of thromocytopenia was reported in a 2-year-old child who developed symptoms of an upper respiratory infection with fever and cough. The patient was treated with aspirin, a product containing triprolidine hydrochloride and pseudoephedrine, and promethazine syrup with dextromethorphan. The attending physician believed that the thromocytopenia was caused by the basic disease process and not by the medications. Leukopenia and thrombocytopenia was reported in a patient receiving promethazine but there are no data provided on the patient's disease state or concomitant drug therapy. On the basis of this limited data it is not possible to determine the cause and effect relationship between promethazine and the blood dyscrasias. Another patient, an 88-year-old male, with an upper respiratory infection who was receiving promethazine, tetracycline and propoxyphene reportedly had hypoplastic anemia secondary to drug reaction. Again, no information on drug dosages or final diagnosis was available and promethazine cannot be determined to cause the hypoplastic anemia.

A further review of adverse reaction reports from the Boston Collaborative Drug Surveillance Program and the University of Florida adverse reaction study shows a low incidence (5.2 percent and 7.1 percent, respectively) of adverse reactions (Ref. 8). The most frequently occurring reactions were drowsiness and confusion or disorientation. In contrast to other phenothiazine derivatives, promethazine showed few incidences of extrapyramidal syndrome (1 of 2,468 patients followed in the studies who received promethazine) and hypotension (3 of 2,468 patients followed in the studies who received promethazine).

Clinical studies (Refs. 1, 9, 10, and 11) indicate that the drug is safe in a dosage effective in allergic rhinitis and authorities in the field of clinical allergy concur (Refs. 12 and 13).

The Panel is aware of the current package insert labeling for promethazine which warns against various possible adverse reactions. These adverse effects are those usually associated with phenothiazine derivatives and clinical experience generally supports their occurrence with most other phenothiazine compounds. According to one authority, jaundice, excessive hypotension or hematopoietic damage have not been reported (Ref. 13). After analysis of published research studies and adverse experience reports on promethazine, however, the Panel concluded that promethazine does not cause the wide range of serious or potentially toxic effects characterizing other members of the chemical class of phenothiazines.

It should be noted that while promethazine is currently available only by prescription, the dosage levels are comparable to those that would be available in OTC use. Therefore, the safety considerations presented to the Panel for prescription marketing have given a reasonably accurate picture of what to expect from OTC use of this ingredient.

The Panel concludes that promethazine hydrochloride is safe for OTC use as an antihistamine in the dosage ranges described below.

(2) *Effectiveness.* In animal studies, promethazine is highly effective in protecting guinea pigs against histamine and the drug is also effective in protecting guinea pigs against anaphylaxis (Ref. 13). Promethazine appears to share with other antihistamine drugs the capacity to suppress rhinorrhea, sneezing and itching but differs from most other antihistamine drugs under consideration in having a longer duration of action. However, no controlled clinical trials appear to have been done to test the effectiveness of promethazine in allergic rhinitis nor in the "common cold". A number of uncontrolled studies indicate that promethazine is effective in the treatment of allergic rhinitis in a dose of 12.5 to 25 mg (Refs. 1, 7, 10, and 13). Based on clinical experience and the data available, the Panel concludes that promethazine is effective when taken in the recommended dosage.

The Panel concludes that promethazine hydrochloride 6.25 mg is the minimum effective OTC dosage for the relief of the symptoms of allergic rhinitis.

(3) *Dosage.* Adult oral dosage is 6.25 to 12.5 mg every 8 to 12 hours not to exceed 37.5 mg in 24 hours. Children 6 to under 12 years oral dosage is 3.125 to 6.25 mg every 8 to 12 hours not to exceed 18.75 mg in 24 hours. Children 2 to under 6 years oral dosage is identified in the labeling section discussed below under professional labeling. For children under 2 years, there is no recommended dosage except under the advice and supervision of a physician.

(4) *Labeling.* The Panel recommends the Category I labeling for antihistamine active ingredients (See part VII. paragraph B.1. below—Category I Labeling.) In addition, the Panel recommends the following specific labeling: (i) *Warning.* "May cause marked drowsiness."

(ii) *Professional labeling.* The Panel recommends that labeling provided to health professionals (but not to the general public) may contain the following additional dosage information: Children 2 to under 6 years oral dosage is 1.56 to 3.125 mg every 8 to 12 hours not to exceed 9.375 mg in 24 hours.

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1. *Pyrilamine maleate.* The Panel concludes that pyrilamine maleate is safe and effective for OTC use in suppressing symptoms of allergic rhinitis as specified in the dosage section discussed below.

(1) *Safety.* Chronic animal toxicity studies done by Winter et al. showed no evidence of a cumulative effect (Ref. 1). In that study, pyrilamine maleate had been administered to rats, dogs and monkeys for varying lengths of time up to 6 months. The following doses appeared to be entirely safe: in rats 10 mg/kg 5 times weekly for 6 months and up to 200 mg/kg daily for 32 days; in dogs, 20 mg/kg 5 times weekly for 6 months, and in monkeys, 50 mg/kg daily for 35 days. No toxic signs nor any hematological, biochemical or pathological abnormalities were found in the animals on these doses.

In human studies, pyrilamine has a low order of toxicity. Side effects are not infrequent but are usually mild. They include drowsiness, listlessness, irritability, and anorexia (loss of appetite) (Ref. 2). In a study by Gay et al., only 3 percent of the 147 patients showed any sign of drowsiness and the incidence of loss of appetite, nausea and vomiting occurred in 27 percent of the patients (Ref. 3).

Two fatalities were reported with pyrilamine maleate. One was of a 21-month-old child who had ingested 600 mg and died 2¾ hours after ingestion, exhibiting a post-convulsive coma. The other fatality was of a 2-year-old child that had ingested 1,400 mg and died during convulsions 4 hours after ingestion (Ref. 4).

The Panel's review of the data supplied by the Food and Drug Administration disclosed a total of two adverse reaction reports on pyrilamine since 1968 (Ref. 5). Both of the adverse reactions were miner and neither was listed as directly related or probably caused by the ingestion of pyrilamine.

The Panel has also considered the most recent data available from the records compiled from Poison Control Centers. (See part VII. paragraph A.6. above—Human toxicity.) Of the 358 suspected poisonings reported for pyrilamine maleate, 18.7 percent exhibited symptoms and 1.7 percent exhibited symptoms serious enough to require treatment or observation at a hospital. There were no fatalities reported with the drug.

The Panel's review of the data supplied by the Food and Drug Administration showed a total of only two adverse reaction reports on pyrilamine since 1968 (Ref. 5). Of the two reports, no adverse reactions were listed as being definitely related to ingestion of pyrilamine; both were listed as possibly related to its ingestion.

The Panel concludes that pyrilamine maleate is safe for OTC use as an antihistamine in the dosage ranges described below.

(2) *Effectiveness.* In vitro and in vivo animal studies indicate that pyrilamine has an intense antihistamine action (Ref. 6) and that the drug has protective activity against histamine and anaphylaxis in the guinea pig (Ref. 7). Pyrilamine and diphenhydramine were equally effective in protecting against anaphylaxis and in preventing histamine-induced contractions of sensitized guinea pig ileum. Winter found in his animal studies that 0.01 mg/kg of pyrilamine protected 100 percent of 19 guinea pigs against a lethal dose of histamine (0.5 mg/kg) for 2 hours (Ref. 1). Gay et al. used the same dose and 91 percent of the guinea pigs were protected for 2 hours (Ref. 3). In this same study, 80 percent of 10 guinea pigs pretreated with 0.1 mg/kg of pyrilamine survived. The pharmacological effects and the histamine antagonism of pyrilamine are comparable to those of chlorpheniramine and similar to those of the other antihistamines (Refs. 1, 6, and 7).

In an uncontrolled study of several antihistaminic drugs including pyrilamine (Ref. 3), this drug was given to 102 patients with allergic rhinitis of whom 70 percent were improved. Two other comparative uncontrolled studies gave similar findings (Refs. 8 and 9) and in a review of the antihistaminic drugs, 66 percent of 604 patients with allergic rhinitis usually receiving a dose of 50 mg were benefited (Ref. 10).

The Panel concludes that pyrilamine maleate 25 to 50 mg is an effective OTC dosage range for the relief of the symtoms of allergic rhinitis.

(3) *Dosage.* Adult oral dosage is 25 to 50 mg every 6 to 8 hours not to exceed 200 mg in 24 hours. Children 6 to under 12 years oral dosage is 12.5 to 25 mg every 6 to 8 hours not to exceed 100 mg in 24 hours. Children 2 to under 6 years oral dosage is identified in the labeling section discussed below under professional labeling. For children under 2 years, there is no recommended dosage except under the advice and supervision of a physician.

(4) *Labeling.* The Panel recommends the Category I labeling for antihistamines. (See part VII. paragraph B.1. below—Category I Labeling). In addition, the Panel recommends the following specific labeling: *Professional labeling:* The Panel recommends that the labeling provided to health professionals (but not to the general public) may contain the following additional dosage information: Children 2 to under 6 years oral dosage is 6.25 to 12.5 mg every 6 to 8 hours not to exceed 50 mg in 24 hours.

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j. *Thonzylamine hydrochloride.* The Panel concludes that thonzylamine hydrochloride is safe and effective for OTC use as an antihistamine in suppressing the symptoms of allergic rhinitis as specified in the dosage section discussed below.

(1) *Safety.* Thonzylamine hydrochloride has been shown in animal experiments to possess antihistaminic activity and a low order of toxicity (Ref. 1). Clinical experience has confirmed that thonzylamine hydrochloride is safe in the dosage ranges used as an antihistamine. Although there are no controlled studies using thonzylamine, the incidence and degree of side effects appear to be less than with most other antihistamines (Refs. 2 and 3). In one report in which patients with "allergies" received an average dose of 50 to 100 mg orally 2 to 4 times daily, investigators in seven separate studies concurred that

thonzylamine was the "least toxic" of the antihistamines then in general use (Ref. 4). In other studies, the incidence of side effects was also low (Refs. 5 through 9) but the dosage of thonzylamine was generally not specified. Of the entire series of 874 patients, an average of 10.9 percent reported side effects which consisted of slight nervousness, headache, gastric disturbance, drowsiness, and dizziness. Most of these side effects were not significant, but the drug was discontinued in a small number of patients due to headache or gastric disturbance.

The Panel has considered the most recent data available from the records compiled from Poison Control Centers during 1973 in which 80 million dosage units were sold. (See part VII. paragraph A.6. above—Human toxicity.) There were no reported suspected poisonings for thonzylamine hydrochloride.

The Panel's review of the data supplied by the Food and Drug Administration showed no adverse reaction reports on thonzylamine hydrochloride since 1968 (Ref. 10).

The Panel concludes that thonzylamine hydrochloride is safe for OTC use as an antihistamine at the dosage ranges described below.

(2) *Effectiveness.* Thonzylamine hydrochloride, administered orally, is generally recognized as possessing antihistamine properties and providing symptomatic relief in allergic rhinitis. However, there are only uncontrolled studies documenting the effectiveness of thonzylamine hydrochloride as an antihistamine.

Most textbooks and several studies (Refs. 5, 7, and 9) indicate thonzylamine hydrochloride has antihistamine action. In a series of uncontrolled studies, 64 percent of patients with "allergy" benefited from oral doses of 50 to 100 mg thonzylamine hydrochloride 2 to 4 times daily (Ref. 4) while in the other studies, thonzylamine was found to be about as effective as other antihistamine drugs. In a review of the antihistamines, thonzylamine 50 mg was reported to have given benefit in 54 percent of 384 patients with allergic rhinitis (Ref. 11). The studies cited suggest that a recommended dosage of 50 to 100 mg up to 4 times a day is effective.

The Panel concludes that thonzylamine hydrochloride 50 to 100 mg is an effective OTC dosage range for the relief of the symptoms of allergic rhinitis.

(3) *Dosage.* Adult oral dosage is 50 to 100 mg every 4 to 6 hours not to exceed 600 mg in 24 hours. Children 6 to under 12 years oral dosage is 25 to 50 mg every 4 to 6 hours not to exceed 300 mg in 24 hours. Children 2 to under 6 years oral dosage is identified in the labeling section discussed below under professional labeling. For children under 2 years, there is no recommended dosage except under the advice and supervision of a physician.

(4) *Labeling.* The Panel recommends the Category I Labeling for antihistamine active ingredients. (See part VII. paragraph B.1. below—Category I Labeling.) In addition, the Panel recommends the following specific labeling: *Professional labeling.* The Panel recommends that labeling provided to health professionals (but not to the general public) may contain the following additional dosage information: Children 2 to under 6 years oral dosage is 12.5 to 25 mg every 4 to 6 hours not to exceed 150 mg in 24 hours.

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Category I Labeling

The Panel recommends the following Category I labeling for antihistamine active ingredients to be generally recognized as safe and effective and not misbranded as well as the specific labeling discussed in the individual ingredient statements:

a. *Indications.* (1) "Alleviates, decreases, or for temporary relief of, running nose, sneezing, itching of the nose or throat and itchy and watery eyes as may occur in allergic rhinitis (such as hay fever)".

(2) "Alleviates, decreases, or for temporary relief of, running nose as may occur in allergic rhinitis (such as hay fever)".

(3) "Alleviates, decreases, or for temporary relief of, sneezing as may occur in allergic rhinitis (such as hay fever)".

(4) "Alleviates, decreases, or for temporary relief of, itching of the nose or throat as may occur in allergic rhinitis (such as hay fever)".

~~(5)~~ "Alleviates, decreases, or for temporary relief of, itchy and watery eyes as may occur in allergic rhinitis (such as hay fever)".

(6) "Dries running nose as may occur in allergic rhinitis (such as hay fever)".

b. *Warnings.* The drowsiness often produced by the antihistaminic drugs is a potential hazard under circumstances in which alertness is important. Therefore the Panel believes that a warning regarding drowsiness should appear on the label for all products containing antihistamine drugs. The Panel believes it is prudent to regard the atropine-like effects of the antihistamines as a possible hazard in patients with glaucoma and as possibly leading to difficulty in urination in those individuals with prostatic hypertrophy. In asthma, the antihistamines may cause drying of bronchial secretions, making expectoration of the secretions more difficult and thereby increasing obstruction of the airway.

Therefore, the Panel recommends that labeling include the following warnings and cautions: (1) For active ingredients not containing the specific warning "May cause marked drowsiness", the statement "May cause drowsiness" should be used.

(2) "May cause excitability especially in children".

(3) "Do not take this product if you have asthma, glaucoma or difficulty in urination due to enlargement of the prostate gland except under the advice and supervision of a physician".

(4) *"Caution.* Avoid driving a motor vehicle or operating heavy machinery".

(5) *"Caution:* Avoid alcoholic beverages while taking this product".

(6) "Do not give this product to children under 6 years except under the advice and supervision of a physician".

There are insufficient data to establish the safety of OTC preparations containing antihistamines in children under 6 years. Individuals vary widely in the degree to which drowsiness, and less commonly, other adverse effects occur when they are given antihistaminic drugs. For this reason, the frequency and severity of side effects cannot be predicted. Respiration may be depressed and this effect can be serious in infections involving the airway. Parents and others may have difficulty assessing the intensity of induced side effects and children cannot be expected to understand their potential hazards. For these reasons, medical supervision is recommended when children under 6 years are given antihistaminic drugs.

2. *Category II conditions under which antihistamine ingredients are not generally recognized as safe and effective or are misbranded.* The use of antihistamines under the following conditions is unsupported by scientific data, and in some instances by sound theoretical reasoning. The Panel concludes that the following labeling should be removed from the market until scientific testing supports their use.

Category II Labeling

The Panel concludes that the use of certain labeling claims related to the safety and/or effectiveness of the product are unsupported by scientific data, and in some instances by sound theoretical reasoning. The Panel has previously discussed such labeling. (See part II. paragraph O. above—CCABA Product Labeling Claims Not Supported by Scientific Evidence.) However, labeling that is de-

scriptive of the product such as its taste or appearance is acceptable.

Unacceptable claims for antihistamines include statements such as the following:

a. *All claims which state or imply a therapeutic action or safety property peculiar to the preparation that cannot be demonstrated in controlled studies.* These include claims such as "specially formulated", "scientifically improved", or "selected", "natural", "extra strength", "teamed components", "superior to ordinary—".

b. *Claims implying a physiological effect which either have no foundation or meaning or will be meaningless or misleading to the public.* Items include: "gets at the root of—"; "fights"; "wakes up"; "recommended by doctors"; "travels through the blood stream".

c. *Claims for relief where time is indeterminate.* Terms include: "fast"; "prompt".

d. *Claims for relief of nasal symptoms (other than running nose, itchy nose, and sneezing).* Terms include: "decreases nasal obstruction"; "decreases nasal congestion"; "relief of stuffy nose (stopped up nose, nasal stuffiness, clogged up nose)".

3. *Category III conditions for which the available data are insufficient to permit final classification at this time.* The Panel concludes that adequate and reliable scientific evidence is not available at this time to permit final classification of the claimed active ingredients listed below. The Panel believes it reasonable to provide 3 years for the development and review of such evidence. Marketing need not cease during this time if adequate testing is undertaken. If adequate effectiveness data are not obtained within 3 years, however, the ingredients listed in this category should no longer be marketed as over-the-counter products. Effectiveness as an antihistamine must be demonstrated by controlled, double-blind studies because of the subjective nature of both the symptoms and the effects of any drug-induced changes.

Category III Active Ingredients

The Panel concludes that the available data are insufficient to permit final classification of the following claimed antihistamine active ingredients:

Phenyltoloxamine citrate
Thenyldiamine hydrochloride (oral)

a. *Phenyltoloxamine citrate.* The Panel concludes that phenyltoloxamine citrate is safe for OTC use but there are insufficient data available regarding its effectiveness to permit final classification as an antihistamine in suppressing the symptons of allergic rhinitis as specified in the proposed dosage section discussed below.

(1) *Safety.* Clinical experience has confirmed that phenyltoloxamine citrate is safe in the dose ranges used as an antihistamine. Animal studies have indicated phenyltoloxamine is one of the least toxic antihistamines. As much as 680 mg/kg given orally to rats produced no symptoms. In dogs, 10 mg/kg for 50 days was well tolerated (Ref. 1).

Studies in humans also suggest a low incidence of side effects at a dosage of 100 to 200 mg in 24 hours with moderate drowsiness occurring following dosage in excess of 200 mg in 24 hours (Ref. 2). One reference states that in therapeutic doses, soporific effects occur in less than 7 percent of patients (Ref. 3). A low incidence of side effects, 6.5 percent, was reported in one study in which allergy patients were given 25 or 50 mg 3 or 4 times daily (Ref. 4). In another study (Ref. 5), phenyltoloxamine was given for its "ataraxic" effect in a dosage of 300 mg daily, 100 mg after lunch for daytime sedation and 200 mg at bedtime for nighttime sedation. Side effects were reported to be minimal in this study.

Sainz (Ref. 6) performed a study in 48 patients to determine side effects and toxicity and found that mild drowsiness appeared at oral doses above 200 mg 4 times daily, or with single doses of 400 mg. Ataxia or abnormal reflexes were not noted at oral doses of 400 mg 4 times a day. There were no extrapyramidal symptoms. The EEG was not affected. A slight blood pressure increase was seen and doses higher than 200 mg 4 times daily produced adrenergic stimulation (increased salivation, gastritis, and diarrhea). Heartburn was found in 14 percent of patients taking the drug, and occasionally nausea was seen. No changes were noted in metabolic, nutritional, endocrine, hematologic, urologic or liver function parameters. Sainz concluded that the drug is not only safe but remarkably free from undesirable reactions at oral doses of the dihydrogen citrate salt of phenyltoloxamine at 100 mg (56 mg of the active moiety) 4 times daily.

The Panel has considered the most recent data available from the records compiled from Poison Control Centers during 1973 in which 423 million dosage units were sold. (See part VII. paragraph A.6. above—Human toxicity.) Of the 90 suspected poisonings reported for phenyltoloxamine citrate, 15.6 percent exhibited some symptoms and 5.6 percent exhibited symptoms serious enough to require treatment or observation at a hospital. There were no fatalities reported with the drug.

The Panel's review of data supplied by the Food and Drug Administration showed only one adverse reaction report on phenyltoloxamine citrate since 1968 (Ref. 7). The adverse reaction was listed as possibly related to abnormal kidney function tests.

The Panel concludes that phenyltoloxamine citrate is safe for OTC use as an antihistamine in the dosage ranges described below.

(2) *Effectiveness.* There are no well-controlled studies documenting the effectiveness of phenyltoloxamine citrate as an antihistamine. Phenyltoloxamine citrate is an antihistamine drug which in animal studies antagonizes most of the pharmacologic actions of histamine (Ref. 1). In clinical use, the drug appears to provide symptomatic relief of allergic symptoms (Refs. 2 and 3), although no controlled studies are available which permit a determination of the minimum effective dosage level.

Cronk and Naumann (Ref. 2) used a dosage of 25 to 50 mg 4 times daily, but reported "relief" only in patients receiving 50 mg 4 times daily. Seyler and Simon (Ref. 4) likewise recommended a dosage of 50 mg 3 or 4 times daily. Thus, clinical experience indicates a daily dosage of 150 to 200 mg.

The Panel concludes that although there are insufficient data to determine that phenyltoloxamine citrate is effective for the relief of the symptoms of allergic rhinitis, 50 mg is the proposed dosage at which this ingredient is most likely effective.

(3) *Proposed dosage.* Adult oral dosage is 50 mg every 4 to 6 hours not to exceed 300 mg in 24 hours. Children 2 to under 12 years oral dosages are identified in the labeling section discussed below under professional labeling. For children under 2 years, there is no recommended dosage except under the advice and supervision of a physician.

(4) *Labeling.* The Panel recommends the Category I labeling for antihistamine active ingredients. (See part VII. paragraph B.1. above—Category I Labeling.) In addition, the Panel recommends the following specific labeling: *Professional labeling.* The Panel recommends that labeling provided to health professionals (but not to the general public) may contain the following additional dosage information: Children 6 to under 12 years oral dosage is 25 mg every 4 to 6 hours not to exceed 150 mg in 24 hours; children age 2 to under 6 years oral dosage is 12.5 mg every 4 to 6 hours not to exceed 75 mg in 24 hours.

(5) *Evaluation.* Data to demonstrate effectiveness will be required according to the guidelines set forth below for testing antihistamine drugs. (See part VII. paragraph C. below—Data Required for Evaluation.)

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(7) OTC Volume 040325.

b. *Thenyldiamine hydrochloride (oral).* The Panel concludes that thenyldiamine hydrochloride (oral) is safe for OTC use but there are insufficient data available regarding effectiveness to permit final

classification as an antihistamine in suppressing the symptoms of allergic rhinitis as specified in the proposed dosage section discussed below.

(1) *Safety.* Clinical experience has confirmed that thenyldiamine hydrochloride (oral) is safe in the dosage ranges used as an antihistamine. The Panel has discussed the topical use of this drug as a nasal decongestant elsewhere in this document. (See part VIII. paragraph B.3.k. below—Thenyldiamine hydrochloride (topical).)

This drug was selected from among several related compounds because of marked antihistaminic and anti-anaphylactic properties and its low toxicity in animals (Refs. 1 and 2). Thenyldiamine is relatively nontoxic in animals. The oral LD_{50} for mice is about 190 mg/kg and for the guinea pig 240 mg/kg. There are no human safety data on the use of thenyldiamine administered orally alone. Data in uncontrolled studies with a combination product containing phenylephrine, acetaminophen and caffeine in addition to thenyldiamine in a dose of 25 to 150 mg daily revealed no significant changes in pulse rate or blood pressure (Refs. 3 and 4). Tabulations of side effects in patients receiving thenyldiamine hydrochloride alone and those receiving the combination formulation are difficult to interpret. The chief side effect appears to be sedation or drowsiness. Dizziness, dryness of the throat, headache, perspiration, and nausea have also been reported (Ref. 1).

The Panel has considered the most recent data available from the records compiled from Poison Control Centers during 1973 in which 2.5 million dosage units were sold. (See part VII. paragraph A.6. above—Human toxicity.) In the one suspected poisoning reported for thenyldiamine hydrochloride, no symptoms were exhibited.

The Panel's review of the data supplied by the Food and Drug Administration showed no adverse reaction reports on thenyldiamine hydrochloride since 1968 (Ref. 5).

The Panel concludes that thenyldiamine hydrochloride is safe for OTC use as an antihistamine in the dosage ranges described below.

(2) *Effectiveness.* There are no well-controlled studies documenting the effectiveness of thenyldiamine hydrochloride (oral) as an antihistamine and reports of clinical experience are lacking. Thenyldiamine hydrochloride was official in U.S.P. XII. The dose was 15 mg orally. The frequency of treatment was not stated. A secondary reference source indicates the dosage to be 15 to 30 mg (Ref. 6). It appears that effective adult dosage may not be attained by using the commercially available OTC combination products which contain 2.5 to 7.5 mg per dosage unit.

In vitro studies of 0.03 gamma thenyldiamine in a 20 ml bath gave 75 percent inhibition of a standardized contraction produced by 0.3 gamma histamine. The drug compared well with diphenhydramine and pyrilamine as measured by histamine shock in the guinea pig where 1 mg/kg gave complete protection against the LD_{100}. The drug also gave marked protection against anaphylaxis in the guinea pig.

The Panel concludes that although there are insufficient data to determine that thenyldiamine hydrochloride (oral) is effective for the relief of the symptoms of allergic rhinitis, 15 to 30 mg are the proposed dosage at which this ingredient is most likely effective.

(3) *Proposed dosage.* Adult oral dosage is 15 to 30 mg every 4 to 6 hours not to exceed 180 mg in 24 hours. Children 2 to under 12 years oral dosages are identified in the labeling section discussed below under professional labeling. For children under 2 years, there is no recommended dosage except under the advice and supervision of a physician.

(4) *Labeling.* The Panel recommends the Category I labeling for antihistamine active ingredients. (See part VII. paragraph B.1. above—Category I Labeling.) However, the Panel recommends that the Category I warning pertaining to use in children be revised from 6 years to 12 years with the following specific labeling: (i) *Warning.* "Do not give this product to children under 12 years except under the advice and supervision of a physician". (ii) *Professional labeling.* The Panel recommends that labeling provided to health professionals (but not to the general public) may contain the following additional dosage information: Children 6 to under 12 years oral dosage is 7.5 to 15 mg every 4 to 6 hours not to exceed 90 mg in 24 hours; children 2 to under 6 years oral dosage is 3.75 to 7.5 mg every 4 to 6 hours not to exceed 45 mg in 24 hours.

(5) *Evaluation.* Data to demonstrate effectiveness will be required according to the guidelines set forth below for testing antihistamine drugs. (See part VII. paragraph C. below—Data Required for Evaluation.)

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Category III Labeling

The Panel concludes that the available data are insufficient to permit final classification of the labeling claims identified below for antihistamines. Additional data are required to substantiate these claims for OTC antihistamine use: a. The following statements of duration are unacceptable unless documentation can specify the number of hours: "provides hours of relief" "all day" "all night".

b. "Alleviates, decreases or for temporary relief of running nose, sneezing, itching of the nose or throat and itchy and watery eyes as may occur in the common cold".

c. "Alleviates, decreases or for temporary relief of running nose as may occur in the common cold."

d. "Alleviates, decreases or for temporary relief of sneezing as may occur in the common cold".

e. "Alleviates, decreases or for temporary relief of itching of the nose or throat as may occur in the common cold".

f. "Alleviates, decreases or for temporary relief of itchy and watery eyes as may occur in the common cold".

g. "Dries running nose as may occur in the common cold".

h. *Claims that sleep will be facilitated.* Terms include "promotes restful sleep".

C. DATA REQUIRED FOR EVALUATION

The Panel has agreed that the protocols recommended in this document for the studies required to bring a category III drug into Category I are in keeping with the present state of the art and do not preclude the use of any advances or improved technology in the future.

1. *Principles in the design of an experimental protocol for testing antihistamine drugs in allergic rhinitis.* a. *General principles.* The antihistaminic drugs are indicated for the symptomatic relief of IgE mediated allergic reactions. (See part II paragraph B.1.—Allergy.) When such reactions occur in the upper airway, the symptoms include sneezing, nasal discharge, nasal obstruction and itching of the nose, eyes, throat and ears. Such symptoms may or may not be accompanied by objective manifestations and for this reason, the patients' subjective sensations must be relied upon in the assessment of drug action. However, observations on the degree of edema of the nasal mucus membrane, the quantity of nasal discharge and the degree of injection of the sclerae may be helpful. The action of this group of drugs is limited to a few hours so that reepated doses at regular intervals are required for a sustained effect. All the antihistamines have side effects which again are subjective and have virtually no objective counterpart. Because of the subjective nature of both the symptoms and the effect of any drug-induced change, double-blind experimental control is especially important in the assessment of antihistaminic drugs.

Considerable experience in assessing therapy for allergic rhinitis caused by pollen (hay fever) has accumulated in the past 15 or more years in the course of efforts to determine the effectiveness of injection therapy (immunotherapy). Hitherto unrecognized problems in the selection of cases, the recording and scoring of symptoms, the tally of medication other than preparation(s) under test and the maintenance of experimental control became apparent (Ref. 1).

b. *Selection of patients.* The selection of patients should be limited of those

giving a clear history of having had allergic symptoms (hay fever) in at least two consecutive annual pollen seasons, who are free from symptoms at other times of the year, who react intensely to prick or scratch test with an extract of the appropriate pollen and who are otherwise in good general health. Patients who are not undergoing treatment with injections of allergenic extracts are preferred in the study.

The diagnosis of allergic rhinitis depends on both a history of the symptoms occurring at the times of allergenic exposure and their absence at other times, and the presence of intense relevant immunologic reactivity commonly determined by skin test. The patient's statements as to the time of year when symptoms occur may be in error. Therefore, documentation of the occurrence of symptoms at the time of exposure and the absence of symptoms at other times by observation of the patient is preferable to the history. Patients who react intensively by skin test to one pollen usually react to several other pollens also. Some of the reactions obtained by skin test may be irrelevant, a positive skin test being a necessary but not sufficient basis for identifying the cause of the symptoms. Thus the limitations of the history and the skin test need to be taken into account.

c. *Methods of study.* Assessment of therapy is based on a subjective response. Therefore, some means of quantitating symptoms must be adopted. Experience has indicated that this can be done satisfactorily by maintaining a daily tally of symptoms specifying type, e.g., sneezing, rhinorrhea, etc., duration in hours per day and intensity. Most patients have little difficulty in describing intensity numerically if they are given an intensity scale wherein points on the scale are defined by statements indicating the degree of discomfort (Refs. 2 and 3). Assignment of a numerical value to the degree of discomfort is space saving and greatly facilitates analysis of the data. However, account should be taken of the burden that a diary imposes on the patient. If too detailed and complicated, patients lose interest and record their symptoms in a perfunctory manner with the result that the data may be worthless. Some compromise between what is ideal and what is practicable must be reached. A satisfactory compromise was one in which the patient was given a symptom score card covering 1 week of study, to be filled out at the end of each day. The patient returned with the card at the end of each week at which time the patient was interviewed and the card rechecked for comprehensibility (Ref. 2). A new card was then supplied.

In a double-blind study which includes a placebo, some patients will suffer severe symptoms and the patient's continuation in the study will thereby be jeopardized. If the design of the study does not permit withdrawal from the study because of severe symptoms as an endpoint, then the investigator will be under great pressure to prescribe or permit use of medication other than the preparations under test or the patient will take medication without reporting having done so. Such medications, if taken, should be recorded accurately on the weekly diary form. Before the study is started, each such drug should be assigned a numerical value per dose based on anticipated efficacy in relieving symptoms of allergic rhinitis. The data may then be incorporated into the analysis at the end of the study.

A placebo identical in appearance and closely similar or identical in taste to the preparation(s) under test must be included in any assessment of drugs for the treatment of allergic rhinitis. Assignment of subjects to the drug(s) under test and the placebo must be random and the code identifying the preparations administered must not be broken until the study is complete.

Patients should be seen throughout the season not less often than every week. Patient diaries should be maintained in which the type, frequency and severity of symptoms and side effects are recorded daily as well as the medication taken. A crossover double-blind design with 30 or more patients is recommended in which each patient takes the test drug or the placebo on alternate weeks. If two dose levels of the test drug are tested, twice the number of patients will be needed.

d. *Interpretation of data.* Results should be subjected to statistical analysis, a p value of 0.05 or less (95 percent confidence or more) being acceptable as evidence of a drug effect. Evidence of drug effectiveness is required from a minimum of three positive studies based on results from three different investigators or laboratories.

All data submitted to the Food and Drug Administration must present both favorable and any unfavorable results.

(5) *Evaluation of safety.* The effect of the drug on the hepatic, renal and other systems should be monitored with particular emphasis on systems expected to be influenced by the drug. In the case of the antihistamines the central nervous system is often affected as indicated by such side effects as drowsiness and fatigue. These should not be induced by the drug at a frequency and intensity which might pose a hazard to the patient in the performance of a daily routine.

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2. *Principles in the design of an experimental protocol for testing antihistamine drugs in the "common cold."* a. *Assessment of the use of antihistaminic drugs for the "common cold."* The antihistaminic drugs have been widely used for the treatment of the symptoms of the "common cold." These drugs are usually marketed in combination products with nasal decongestant drugs. It is the Panel's view that this use of the antihistaminic drugs has been based predominantly on clinical impressions and uncontrolled clinical trials, the first of which was published by Brewster in 1947 (Ref. 1). On the other hand, a number of trials have been conducted with double-blind experimental controls but have failed for the most part to substantiate claims for effectiveness. These negative results indicate that if the antihistaminic drugs indeed have a favorable effect on the symptoms of the "common cold," this effect must be of a relatively low order. The subject has been recently reviewed (Ref. 2). The Panel concurs with the authors who stated:

> Many of the reports favoring antihistamine use were published some years ago when a well-controlled, randomized, double-blind clinical trial was not generally recognized as important in the evaluation of therapy. However, results supporting antihistamine use should be interpreted with caution when the research goals are imprecise and the study design permits biases. On the other hand, the findings of the less favorable reports that antihistamines appear not to prevent, abort, or relieve the symptoms of a cold, are supported by only a slightly greater specificity of definition and increased rigor of research methodology. Of all the reports, only two combined precision in definitions and controlled design; their conclusions did not support the use of antihistamines to prevent or relieve the symptoms of a cold. The general lack of specificity in defining disease and research goals and lack of rigor in research design in the majority of all studies is noteworthy. In short, there appears to be little valid evidence that antihistamines have any effect on the common cold.

Studies on the efficacy of the antihistaminic drugs in the treatment of the "common cold" may be misleading if the means of selection do not minimize inadvertent inclusion of subjects with allergic rhinitis, the symptoms of which are similar to those of the "common cold." Relief of symptoms will then be erroneously ascribed to favorable effect of the antihistaminic drugs on the symptoms of the "common cold" when indeed the observed benefit may be attributable to the known efficacy of the antihistaminic drugs in allergic rhinitis. The Panel has earlier discussed in this document both the "common cold" and allergic rhinitis. (See part II. paragraph B.3. above—The "common cold" and part II. paragraph B.6.a. above—Allergic rhinitis.)

The Panel concludes that the effectiveness of the antihistaminic drugs in relieving or allaying the symptoms of the "common cold" has not been established. If further studies on the effectiveness of the antihistaminic drugs in the treatment of the "common cold" are to be carried out, the Panel suggests that particular attention be directed to the selection of subjects and the means of recording symptoms using groups of patients large enough to give statistically meaningful results.

b. *General principles.* The symptoms of allergic rhinitis and the "common cold" have many similarities. A watery

nasal discharge is characteristic of allergic rhinitis and is usual in the "common cold" in the first 1 to 3 days. Sneezing is likewise common to both. Itching of the nose and eyes is more common in allergic rhinitis but also occurs in the "common cold." Nasal congestion occurs in both conditions. Coughing is not a frequent symptom of allergic rhinitis but it occurs in a small percent of cases. Cough likewise occurs in the "common cold," usually in the latter phase of the illness. Fever of low degree may occur in the "common cold," but it is not frequently present. Fever is absent in allergic rhinitis. Watering and redness of the eyes may occur in both conditions (Refs. 3, 4, and 5).

It is commonly stated in texts on allergic disease that examination of the patient with allergic rhinitis reveals swelling within the nose (swollen turbinates) which has a bluish or gray color (Ref. 5), whereas in the "common cold" their color is red (Ref. 4). No studies have been done to test the frequency with which this distinction is diagnostic and its reliability as a means of selecting patients for inclusion in a study of antihistaminic drugs in the treatment of the "common cold" remains uncertain. No other finding on examination appears to be useful in distinguishing between the early phases of the "common cold" and allergic rhinitis.

Because the symptoms of allergic rhinitis and the "common cold" are so similar, the two conditions are readily confused. The reported efficacy of the antihistaminic drugs in the treatment of the "common cold" has been attributed to the inadvertant inclusion of some cases of allergic rhinitis in some studies (Ref. 2) in which condition the antihistaminic drugs are recognized as effective. Unless steps are taken to eliminate subjects with allergic rhinitis from the study population, the results of the study of the "common cold" may be misleading.

c. *Selection of patients.* Since the distinction between allergic rhinitis and the "common cold," especially in its early phases, is difficult or impossible to make on the basis of symptoms and examination, the following means of minimizing inclusion of subjects with symptoms of allergic rhinitis should be adopted:

(1) Subjects giving a history of allergic rhinitis, e.g., hay fever or allergy to animals, should be excluded.

(2) Studies should be done in the months when allergic exposure is less likely and the "common cold" is more prevalent.

Selection of subjects according to these principles will minimize but cannot entirely eliminate the inclusion of some subjects who are having symptoms of allergic rhinitis and not a "common cold."

Subjects selected for the studies should be in good health except for the presence of a "common cold." The symptoms to be evaluated, i.e., runny nose, sneezing, etc., should have been present for 1 day but not longer than 3 days. Fever should be absent or should not exceed 100° F by mouth (adults) or 101° F by mouth (children under 12 years). Those with evidence of bacterial infection of the pharynx (exudative pharyngitis) or who have severe pharyngitis and severe sore throat should be excluded.

d. *Methods of study.* The drug(s) to be tested and a placebo should be identical in appearance and closely similar in taste identifiable by code only. Strict double-blind control throughout the study is essential. The groups of subjects should be matched by age, sex and severity and duration of illness.

Each group should contain 50 to 100 subjects. This large number is considered mandatory for the following reasons: a crossover design is not possible in so short an illness; the assessment is based on a subjective response; there are uncertainties in diagnosis; there is possible heterogeneity of the study population with respect to the type of virus causing the illness; and the effect of the antihistaminic drug in relieving symptoms of the "common cold" is not marked.

Medication other than the preparations in the test should not be taken during the course of the study. The design of the study should be such as to permit determination of each preparation's effect on each type of symptom and the stage in the disease in which this effect takes place. Therefore, each subject should maintain an appropriate tally of the type, duration and intensity of symptoms. The study should be of sufficient length to encompass the entire illness to provide data on all possible effects of the drug under test on the course of the disease. If a subject drops out of the study, the reason for doing so should be determined and recorded.

All data submitted to the Food and Drug Administration must present both favorable and any unfavorable results.

e. *Interpretation of data.* A recommended dose of the antihistamine should induce a statistically significant reduction in symptoms when compared to the placebo response. Results should be subjected to statistical analysis, a p value of 0.05 or less (95 percent confidence or more) being acceptable as evidence of a drug effect. A decision on drug effectiveness should be based on demonstrable drug effectiveness in a minimum of three positive comparable double-blind studies based on results from three different investigators or laboratories.

f. *Evaluation of safety.* If the safety of the drug has not been established, then the effect of the drug on the hepatic, renal and other systems should be monitored with particular emphasis on systems expected to be influenced by the drug. In the case of the antihistamines, the central nervous system is often affected, as indicated by such side effects as drowsiness and fatigue. These should not be induced by the drug at a frequency and intensity that might pose a hazard to the patient in the performance of a daily routine.

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VIII. NASAL DECONGESTANTS

A. GENERAL DISCUSSION

A nasal decongestant is an agent which reduces nasal congestion in patients with acute or chronic rhinitis. These agents may be administered topically as drops, sprays or inhaled vapors or orally in a solid or liquid dosage form. The drug effect is brought about by constriction of dilated blood vessels (vasoconstriction) within the nasal mucosa, thus temporarily reducing the swelling associated with inflammation of the mucous membrane lining the nasal passage (Ref. 1).

Topically administered nasal decongestants produce an intense degree of vasoconstriction, a factor responsible for the rapid and pronounced reduction in nasal obstruction. This intense local vasoconstriction also accounts for negligible absorption of the nasal decongestant into the general circulation. Consequently, negligible systemic effects occur following topical use of nasal decongestants unless excessive nasal solution is applied causing drainage into the stomach where it may be absorbed. Studies demonstrating minimal systemic absorption of radioactively labeled oxymetazoline following intranasal application (Ref. 2) and negligible cardiovascular effects following normal and excessive intranasal doses of phenylephrine or xylometrazoline (Refs. 3 through 7) support this point. Because of the remarkable degree of nasal decongestion which follows topical application of these agents, there is the tendency on the part of patients to administer nasal decongestants too frequently and for too long a period of time. Continued and intense drug-induced vasoconstriction can lead to rebound dilation of the blood vessels as the drug effect subsides. This phenomenon, which intensifies nasal congestion and perpetuates the rhinitis condition, has been termed "rebound congestion." This problem is minimized if topically applied decongestants are administered in accordance with label directions at recommended intervals for periods not exceeding 3 days.

Another practical caution with the use of topically applied decongestants is in regard to the possible spread of infection if the drug dispenser is used by more than one person. This can occur if the tip of the dropper or spray container comes in contact with the nose during drug administration.

Some of the nasal decongestants (sympathomimetic amines) are also effective when administered orally. Although the intensity of vasoconstriction in the nasal mucosa and associated symptomatic re-

lief of nasal congestion are less than that produced by the topical application of decongestants, the problem of rebound congestion is not a factor with use of the orally administered nasal decongestants. These orally administered sympathomimetic amines are distributed by the circulation to other target tissues as well as the nasal mucosa and thus produce side effects not seen following use of nasal decongestants topically.

In general, side effects associated with recommended oral doses of OTC nasal decongestants are minimal, but at higher doses may include nervousness, dizziness, and sleeplessness. Individuals with disease conditions which can be aggravated by sympathomimetic drug action, e.g., high blood pressure, heart disease, diabetes mellitus and hyperthyroidism, should not use decongestants orally except under the advice and supervision of a physician. Likewise, patients taking other drugs whose action can intensify the sympathomimetic drug action, e.g., monoamine oxidase inhibitors, should not take nasal decongestants orally except under the advice and supervision of a physician. The Panel does not feel these restrictions should apply to topically applied nasal decongestants when administered in recommended doses because of their localized action, i.e., minimal systemic absorption.

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B. CATEGORIZATION OF DATA

1. *Category I conditions under which nasal decongestant ingredients are generally recognized as safe and effective and are not misbranded.*

Category I Active Ingredients

The Panel has classified the following nasal decongestant active ingredients as generally recognized as safe and effective and not misbranded:

Ephedrine preparations (topical): Ephedrine, Ephedrine hydrochloride, Ephedrine sulfate, Racephedrine hydrochloride
Naphazoline hydrochloride (topical)
Oxymetazoline hydrochloride (topical)
Phenylephrine hydrochloride (oral/topical)
Phenylpropanolamine preparations (oral): Phenylpropanolamine bitartrate, Phenylpropanolamine hydrochloride, Phenylpropanolamine maleate
Propylhexedrine (inhalant)
Pseudoephedrine preparations (oral): Pseudoephedrine hydrochloride, Pseudoephedrine sulfate
Xylometazoline hydrochloride (topical)

a. *Ephedrine preparations (ephedrine, ephedrine hydrochloride, ephedrine sulfate, racephedrine hydrochloride) (topical)*. The Panel concludes that ephedrine and its salts are safe and effective as topical nasal decongestants for OTC use as specified in the dosage section discussed below.

(1) *Safety.* Clinical experience has confirmed that ephedrine and its salts (topical) are safe in the dosage ranges used as nasal decongestants. Having been introduced from China in 1924 (Ref. 1) there has been a long experience with this drug which is used orally, chiefly from bronchodilation and usually in a dosage of 25 mg 4 times daily and topically in the nose as a 0.5 percent to 3 percent solution (Ref. 2). No reports describing adverse effects when used topically were encountered nor were there studies directed at the question of adverse local effects. Based on general clinical experience with topical nasal decongestants, rebound congestion would be expected with continued use. However, concentrations of 1 percent or less, as judged by the clinical experience of the Panel, would not be expected to cause this reaction if use is limited to a few days.

(2) *Effectiveness.* Extensive clinical experience indicates that ephedrine and its salts in 0.5 to 1 percent concentrations applied as drops or spray have a nasal decongestant effect (Ref. 3). Ephedrine as a prototype of the topical sympathomimetic nasal decongestant agents has been compared to other effective topical nasal decongestants in both objective measurement studies (Ref. 4) and subjective observation of nasal decongestant activity (Refs. 5 and 6) in patients with acute rhinitis. Ephedrine sulfate in 1 percent solution has been demonstrated to induce a prompt nasal decongestant effect which persists at maximal levels for up to 1 hour and gradually declines to pretreatment levels by the 4th hour.

(3) *Dosage.* Adult topical dosage is 2 to 3 drops or sprays in each nostril of a 0.5 percent aqueous solution not more frequently than every 4 hours. Children 6 to under 12 years topical dosage is 1 to 2 drops or sprays of a 0.5 percent solution not more frequently than every 4 hours. For children under 6 years, there is no recommended dosage except under the advice and supervision of a physician.

(4) *Labeling.* The Panel recommends the Category I labeling for nasal decongestant active ingredients (see part VIII. paragraph B.1. below—Category I Labeling). In addition, the Panel recommends the following specific labeling: *Warning:* "Do not give this product to children under 6 years except under the advice and supervision of a physician".

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b. *Naphazoline hydrochloride (topical)*. The Panel concludes that naphazoline hydrochloride is safe and effective as a topical nasal decongestant for OTC use as specified in the dosage section discussed below.

(1) *Safety.* Clinical experience has confirmed that naphazoline hydrochloride (topical) is safe in the dosage ranges used as a nasal decongestant. Studies involving visualization of the nasal mucosa following a single application of naphazoline, 0.05 to 0.1 percent, revealed rebound congestion as a fairly consistent sequel to the 4 to 6 hour period of nasal decongestion (Refs. 1 and 2). The tendency for frequent and continued use due to rebound congestion has been reported by several authors (Refs. 3 through 6). The continued use of naphazoline hydrochloride may result in dependence. To avoid this dependence, naphazoline use should not exceed 3 days duration.

In infants and young children, nasal administration as well as accidental ingestion of 0.05 to 0.1 percent naphazoline have been associated with systemic effects such as sedation, nervousness, increase in systolic blood pressure and bradycardia (Refs. 7 through 13). Furthermore, because rebound congestion with naphazoline is also a problem in infants, this nasal decongestant should probably not be used in children under 6 years (Ref. 1). For children 6 to 12 years, the pediatric concentration of 0.025 percent, should be used to minimize exposure to excess quantities of the drug.

(2) *Effectiveness.* Single dose applications of naphazoline, 0.1 percent in adult rhinitis patients using objective meas-

urement, revealed onset of nasal decongestion within 10 minutes and persisting up to 6 hours (Refs. 2 and 14). A single-dose objective measurement study in children demonstrated nasal decongestion of up to 5 hours duration (Ref. 1). The number and ages of the children and the concentration of naphazoline were not specified. In one study involving repeated administration of 0.05 percent naphazoline drops over a 1-week period, 34 of 35 patients experienced satisfactory nasal decongestion as judged subjectively by the patient and by visualization of the nasal mucosa (Ref. 15).

(3) *Dosage.* Adult topical dosage is 1 to 2 drops or sprays of a 0.05 percent aqueous solution in each nostril not more frequently than every 6 hours. Children 6 to under 12 years topical dosage is 1 to 2 drops or sprays of a 0.025 percent aqueous solution in each nostril not more frequently than every 6 hours. For children under 6 years, there is no recommended dosage except under the advice and supervision of a physician.

(4) *Labeling.* The Panel recommends the Category I labeling for nasal decongestant active ingredients. (See part VIII. paragraph B.1. below—Category I Labeling.) In addition, the Panel recommends the following specific labeling: *Warnings.* (i) *For products containing a concentration of 0.025 percent naphazoline hydrochloride:* "Do not give this product to children under 6 years except under the advice and supervision of a physician".

(ii) *For products containing a concentration of 0.05 percent naphazoline hydrochloride:* "For adult use only. Do not give this product to children under 6 years since it may cause sedation if swallowed".

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c. *Oxymetazoline hydrochloride (topical).* The Panel concludes that oxymetazoline hydrochloride is safe and effective as a topical nasal decongestant for OTC use as specified in the dosage section discussed below.

(1) *Safety.* Clinical experience has confirmed that oxymetazoline hydrochloride (topical) is safe in the dosage ranges used as a nasal decongestant. Because the decongestant effect of oxymetazoline hydrochloride administered as drops or spray persists up to 5 to 6 hours and gradually declines thereafter, rebound congestion after single administration is negligible (Ref. 1). Twice a day dosing which should give adequate relief of nasal congestion should be expected to have a negligible incidence of rebound congestion. Several studies in adults with chronic rhinitis using either 0.05 percent drops or spray for 2 days to 4 weeks support this contention (Refs. 2 through 5). In one study 92 chronic rhinitis patients used 0.05 percent oxymetazoline spray in one nostril and 0.25 percent phenylephrine spray in the other nostril for 2 weeks. In this double-blind study rebound congestion was subjectively noted in one-third of the oxymetazoline-treated nostrils and two-thirds of the phenylephrine-treated nostrils (Ref. 6). No rebound congestion was noted over a 6 hour observation period following 5 drops of 0.025 percent oxymetazoline in each nostril of 33 children with allergic rhinitis (Ref. 7). In 30 children ages 4 to 10 years with allergic rhinitis, treatment with 0.025 percent oxymetazoline, 3 drops in each nostril 3 times a day, was associated with no loss of effectiveness during a 2-week treatment period as measured by electronic posterior rhinometry and no rebound congestion in a 2 week posttreatment evaluation period (Ref. 8).

Animal studies with radioactively labeled oxymetazoline indicate that the rate of systemic absorption from nasal application is too slow to achieve pharmacologic levels in the plasma (Ref. 9). Furthermore, double-blind studies in healthy adults reveal that 1.8 mg, the equivalent of 3.6 ml of a 0.05 percent solution, was the minimal orally administered dose of oxymetazoline producing any measurable effect on the cardiovascular system. Nonspecific EKG changes were not accompanied by blood pressure or heart rate changes (Ref. 10).

Because of these safety considerations the Panel recommends that oxymetazoline, which is currently a drug available only by prescription, be reclassified to permit OTC use as well.

(2) *Effectiveness.* In a double-blind subjective evaluation study, 92 adult patients with chronic rhinitis judged oxymetazoline, 0.05 percent spray, to induce nasal decongestion of 4 to 8 hours duration (Ref. 6). Objective studies in 20 patients with either chronic rhinitis due to allergy or acute rhinitis due to head cold showed effectiveness of a 0.05 percent oxymetazoline spray in two-thirds of the patients with airways still twice pretreatment size at the end of 6 hours (Ref. 1).

In a double-blind subjective evaluation study in 14 children, 2 to 6 years of age with allergic rhinitis, complete opening of the nasal airway was restored for 9 to 12 hours in 7 of the 14 patients receiving 1 drop of 0.025 percent oxymetazoline solution per nostril 2 times daily (Ref. 11). Objective studies in 30 children with allergic rhinitis, ages 4 to 10 years, receiving 0.025 percent oxymetazoline, 3 drops per nostril 3 times daily revealed persistent effectiveness over a 2-week treatment period (Ref. 8).

(3) *Dosage.* Adults and children 6 to under 12 years topical dosage is 2 to 3 drops or sprays of a 0.05 percent aqueous solution in each nostril 2 times daily (in the morning and evening). Children 2 to under 6 years topical dosage is 2 to 3 drops of a 0.025 percent aqueous solution in each nostril 2 times daily (in the morning and evening). Only drops should be used in children 2 to under 6 years since the spray is difficult to use in the small nostril. For children under 2 years, there is no recommended dosage except under the advice and supervision of a physician.

(4) *Labeling.* The Panel recommends the Category I labeling for nasal decongestant active ingredients. (See part VIII. paragraph B.1. below—Category I Labeling).

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d. *Phenylephrine hydrochloride (oral/topical)*. The Panel concludes that phenylephrine hydrochloride is safe and effective as an oral and as a topical nasal decongestant for OTC use as specified in the dosage section discussed below.

(1) *Safety.* (i) *As an oral nasal decongestant:* Clinical experience has confirmed that phenylephrine hydrochoride is safe in the dosage ranges used as an oral nasal decongestant.

Key and Violante reported that oral doses of 40 to 60 mg phenylephrine are necessary for consistent clinically meaningful cardiovascular effects such as increased diastolic pressure and reflex cardiac slowing (Ref. 1). Various reports reinforce the impression that in normal volunteers, blood pressure and pulse rate responses to 10 to 15 mg oral doses are equal to or only minimally greater than placebo. The maximum blood pressure increase does not exceed 2 to 7 mm Hg and the pulse rate changes do not exceed ±6 beats/minute. At doses of 25 mg, blood pressure increases up to 7 mm Hg and pulse changes of ±4–13 beats per minute were occasionally noted at some time intervals (Refs. 1 through 11). If patients were also receiving MAO inhibitors, however, even 10 mg doses of phenylephrine can induce clinically significant cardiovascular responses (Ref. 12).

Overtly perceived side effects at 10-mg doses approximate the incidence and pattern of a placebo response, whereas 15 to 25-mg doses are associated with an increasing incidence of symptoms related to mild central nervous system stimulation (Ref. 1).

(ii) *As a topical nasal decongestant:* Clinical experience has confirmed that phenylephrine hydrochloride is safe in the dosage ranges used as a topical nasal decongestant. Gundrum, Stambuck and Gaines reported a study in which supratherapeutic doses of 0.25 percent phenylephrine drops were chronically administered to rabbits (Ref. 13). The animals were given drops in each nostril either 3 times daily for 10 days or 10 times daily for 3 days. Examination of nasal tissue sections removed from these treated animals revealed no gross or microscopic changes from normal nasal mucosa.

Objective measurement studies showed transient rebound congestion in 3 of 12 adult rhinitis patients during 3 days of treatment with 0.5 percent phenylephrine spray (Ref. 14). Two thirds of 92 chronic rhinitis patients using 0.25 percent phenylephrine spray for 2 weeks noted rebound congestion (Ref. 15). Rhinoscopic observation revealed rebound congestion in 4 of 33 children following single doses of 0.25 percent phenylephrine drops, 5 drops in each nostril (Ref. 16).

Groups of patients with either cardiac, hypertensive and hyperthyroid disorders or diabetes mellitus were administered 5 drops of 0.25 percent or 1 percent phenylephrine solution into each nostril remaining in a head-low position for several minutes to maximize contact time (Refs. 17 and 18). No marked changes in blood pressure control readings were noted over a 45-minute observation period.

(2) *Effectiveness.* (i) *As an oral nasal decongestant:* Clinical studies have documented the effectiveness of phenylephrine as an oral nasal decongestant.

A series of five double-blind crossover placebo-controlled studies over a 3-year period in one laboratory revealed oral doses of phenylephrine from 5 to 25 mg to induce objectively measurable nasal decongestion when compared to placebo in patients with head cold as determined by an anterior rhinometry procedure (Refs. 5 through 9, and 19). Onset time was in 15 to 20 minutes with a duration of 2 to 4 hours. Maximum nasal decongestant effect was associated with the 25 mg dose. Two other laboratories conducted five similarly designed experiments, but because of greater apparent placebo response and variability in inpatient response the studies could not demonstrate a statistically significant difference of 10 to 25 mg from placebo (Refs. 20 through 24).

Subsequent studies measuring nasal airway resistance in head cold patients demonstrated significant nasal decongestant responses to 10 to 25 mg phenylephrine (Ref. 10). In these studies, 25 mg induced a maximal reduction of nasal resistance approaching that reported for noncongested normals, and 10 to 15 mg doses were clinically equivalent in inducing a decrease of nasal resistance about ⅔ maximal. Onset of these effects occurred within 15 minutes. The maximum effect occurred within 30 to 90 minutes with a gradual decline thereafter. A double-blind crossover study in 20 chronic rhinitis patients, however, could demonstrate no significant decrease in nasal airway resistance as compared to placebo with 10, 20, or 40 mg of phenylephrine, orally, over a 4-hour observation period (Ref. 25). In this study, phenylpropanolamine 40 mg and pseudoephedrine 60 mg each produced a significant decrease in nasal airway resistance persisting for at least 3 hours.

A recent double-blind controlled study involving 50 adult patients with nasal congestion associated with the "common cold" (25 patients in each group) demonstrated that a single oral 10 mg dose of phenylephrine led to a reduction in nasal airway resistance averaging 11 percent at 15 minutes, 21 percent at 30 minutes, 28 percent at 60 minutes and 26 percent at 120 minutes (Ref. 26). These reductions were all significantly different from placebo at the corresponding measurement times. These 50 patients were part of a 200-patient subjective evaluation study group with nasal congestion associated with the "common cold", 100 of each who received either 10 mg phenylephrine or placebo at 4-hour intervals over a 12-hour period. Patient subjective evaluation revealed that the phenylephrine treatment group experienced relief of nasal congestion, runny nose and sneezing throughout the 12-hour observation period. Symptom relief in each case was significantly different from that reported by the placebo group (Ref. 26).

(ii) *As a topical nasal decongestant:* In a double-blind crossover placebo-controlled study, phenylephrine was given as a 0.5 percent spray, 1 spray in each nostril repeated in 3 minutes, to one group of 16 patients with head cold and one group of 9 patients with allergic rhinitis. Objective measurements using both posterior electronic rhinometry and body plethysmography revealed significant nasal decongestion at the 30- and 60-minute recording times (Ref. 27).

In another study using 0.5 percent phenylephrine spray in 12 adult rhinitis patients, objectively measured nasal decongestant effects persisted from 1 to 3 hours following administration (Ref. 14). In a 2-week subjective evaluation study of phenylephrine 0.25 percent spray in 92 chronic rhinitis patients, the duration of effect following each dose was generally reported to be 4 hours or less (Ref. 15).

(3) *Dosage.* (i) *As an oral nasal decongestant:* Adult oral dosage is 10 mg every 4 hours not to exceed 60 mg in 24 hours. Children 6 to under 12 years oral dosage is 5 mg every 4 hours not to exceed 30 mg in 24 hours. Children 2 to under 6 years oral dosage is 2.5 mg every 4 hours not to exceed 15 mg in 24 hours. For children under 2 years, there is no recommended dosage except under the advice and supervision of a physician.

(ii) *As a topical nasal decongestant:* Adult topical dosage is 2 to 3 drops or sprays in each nostril of a 0.25 to 0.5 percent aqueous solution not more frequently than every 4 hours. Children 6 to under 12 years topical dosage is 2 to 3 drops or sprays in each nostril of a 0.25 percent aqueous solution not more frequently than every 4 hours. Children 2 to under 6 years topical dosage is 2 to 3 drops in each nostril of a 0.125 percent aqueous solution not more frequently than every 4 hours. Only drops should be used in children 2 to under 6 years since the spray is difficult to use in the small nostril. For children under 2 years, there

is no recommended dosage except under the advice and supervision of a physician.

(4) *Labeling.* (1) *As an oral nasal decongestant:* The Panel recommends the Category I labeling for nasal decongestant active ingredients. (See part VIII. paragraph B.1. below—Category I Labeling.)

(ii) *As a topical nasal decongestant:* The Panel recommends the Category I labeling for nasal decongestant active ingredients. (See part VIII. paragraph B.1. below—Category I Labeling.) In addition, the Panel recommends the following specific labeling: *Warnings:* (*a*) *For products containing a concentration of 0.125 percent phenylephrine hydrochloride:* "Do not give this product to children under 2 years except under the advice and supervision of a physician".

(*b*) *For products containing a concentration of 0.25 percent phenylephrine hydrochloride:* "Do not give this product to children under 6 years except under the advice and supervision of a physician".

(*c*) *For products containing a concentration of 0.5 percent phenylephrine hydrochloride:* "For adult use only. Do not give this product to children under 12 years except under the advice and supervision of a physician".

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e. *Phenylpropanolamine preparations (phenylpropanolamine bitartrate, phenylpropanolamine hydrochloride, phenylpropanolamine maleate) (oral).* The Panel concludes that phenylpropanolamine and its salts are safe and effective as oral nasal decongestants for OTC use as specified in the dosage section discussed below.

(1) *Safety.* Clinical experience has confirmed that phenylpropanolamine and its salts (oral) are safe in the dosage ranges used as nasal decongestants. Phenylpropanolamine is one of the most frequently used oral nasal decongestants, similar in action to ephedrine but with less central nervous system stimulation (Ref. 1). Subjective evaluation studies reveal that, in adults, phenylpropanolamine in plain capsules in doses up to 50 mg every 3 hours is associated with overt side effects either equal to or only slightly exceeding those of placebo. The side effects consisted of nervousness, insomnia, motor restlessness and nausea (Refs. 2 and 3).

Boyer reported three patients with prostatic hypertrophy who complained of urinary retention following ephedrine dosing but had no urinary retention at effective nasal decongestant doses of phenylpropanolamine (Ref. 3).

In three reports involving a total of over 200 children ages 2 to 15, phenylpropanolamine, in age-related doses of 6.25 to 25 mg 4 times daily in combination with acetaminophen and in one study also with phenyltoloxamine, was subjectively observed to relieve symptoms of nasal congestion with a low incidence of side effects (Refs. 4 through 6).

Individuals with normal blood pressure receiving phenylpropanolamine alone, either as a 50 mg plain capsule 4 times daily or as a 50 mg sustained release capsule 2 times daily had no significant effect on blood pressure or pulse rate. No adverse effect on cardiovascular systems was noted after 5 to 42 days of treatment (Refs. 7 through 10). Intravenous administration of phenylpropanolamine induced dose-related systolic blood pressure increases in humans. A 16 to 28 mm increase following 20 to 25 mg and a 44 to 82 mm increase following 50 mg were observed (Ref. 11).

Phenylpropanolamine 50 mg, in sustained release combination with belladonna alkaloids 0.2 mg, and chlorpheniramine 4 mg, was administered 2 times daily for 7 days to groups of patients with normal anterior chamber angle, with narrow angle but no glaucoma signs and to patients with frank glaucoma controlled by medication. No drug-induced alteration of intraocular tension was evidenced in any of the 3 groups of subjects (Refs. 12 and 13).

There have been isolated "letter to the editor" reports of individuals consuming therapeutic doses of phenylpropanolamine-containing preparations and experiencing an acute hypertensive episode (Ref. 14). Details relative to other contributing factors are usually too vague to determine if the phenylpropanolamine was entirely responsible. One "letter" reported an acute overdose of a sustained release phenylpropanolamine combination product, eight spansules containing 50 mg of phenylpropanolamine in combination with isopropamide and diphenylpyraline, was followed within 2 hours by an acute hypertensive response, severe headaches, restlessness and vomiting (Ref. 15).

One paper cited three cases of "psychotic episodes" associated with presumably therapeutic doses of phenylpropanolamine 50 mg, in combination with isopropamide and phenyltoloxamine (Ref. 16). The authors indicated that personality changes following phenylpropanolamine preparations were not an uncommon occurrence in patients in their hospitals.

In summary then, at therapeutic doses of phenylpropanolamine taken orally, the incidence of side effects in adults and

children is low. There have been isolated reports, however, of individuals experiencing idiosyncratic reactions of central nervous system stimulation and/or blood pressure rise following therapeutic doses. These effects would also be expected in most individuals with acute overdoses of the drug.

Prior MAO inhibitor treatment has been clearly shown to potentiate dangerously the blood pressure elevating effects of 30 to 50 mg phenylpropanolamine (Refs. 17 through 20).

A single incident was reported of phenylpropanolamine 50 mg, in combination with chlorpheniramine and isopropamide, antagonizing the antihypertensive effect of bethanidine sulfate, an analogue of guanethidine sulfate (Ref. 21). The antihypertensive effect of guanethidine can be antagonized by concurrent administration of amphetamine (Ref. 22). Current evidence suggests that phenylpropanolamine, being structurally similar to amphetamine, might be expected to exert a similar antagonistic effect (Ref. 23). However, this effect is important to note but not sufficiently documented to elicit a warning statement.

(2) *Effectiveness.* Three of five objective, double-blind, crossover studies comparing phenylpropanolamine with placebo in patients with chronic nasal congestion have demonstrated oral nasal decongestant effectiveness in 25 to 40 mg doses.

The earliest report, using anterior rhinometry in 88 patients, some with acute and some with chronic nasal congestion, showed that ephedrine sulfate 25 mg, orally was significantly better than placebo at the 1-hour time period; but phenylpropanolamine hydrochloride 25 mg, as well as pseudoephedrine hydrochloride, 60 mg, and phenylephrine hydrochloride 10 mg, were not significantly different from placebo. In this crossover study the patients were tested on 5 consecutive days (Ref. 24).

The second study measuring in 12 patients nasal airway resistance at a flow rate of 0.5 l/second demonstrated phenylpropanolamine hydrochloride 18 mg orally to yield greater reduction in nasal airway resistance from pre-drug state than placebo throughout a 4-hour period of observation. The validity of these results is unclear since acetaminophen 325 mg orally also induced a similar magnitude of response in this test (Ref. 25).

A similar followup study in 12 patients by the same author did show significant difference between phenylpropanolamine 25 mg orally and placebo during a 4-hour observation period (Ref. 26).

This author then compared 3 successive doses of 25 mg at 4-hour intervals with a single 75-mg dose in a timed-release formulation in a crossover design in 12 patients and demonstrated continued reduction in nasal airway resistance throughout a 13-hour test period in both cases (Ref. 27). Urinary excretion of phenylpropanolamine, administered as a 75-mg timed-release capsule, approximates 3 doses of 25 mg administered at 4-hour intervals (Ref. 28). Although blood level data more directly reflect rate of drug absorption and drug level at sites of action, these urinary excretion data are consistent with the sustained decrease in nasal airway resistance obtained with a 75 mg timed-release capsule and three consecutive doses of 25 mg.

Another investigation measuring nasal airway resistance at a flow rate of 0.2 l/second in trained volunteers, demonstrated that phenylpropanolamine 40 mg orally induces a peak affect up to 3 hours with gradual return toward control thereafter (Refs. 29 and 30). This investigator also demonstrated that a timed-release formulation of phenylpropanolamine hydrochloride 50 mg in combination with belladonna alkaloids 0.2 mg and chlorpheniramine maleate 4 mg induced a significant decrease in nasal resistance compared to placebo over a 10-hour testing interval (Ref. 31).

(3) *Dosage.* Dosages are based on the phenylpropanolamine hydrochloride equivalent. Adult oral dosage is 25 mg every 4 hours or 50 mg every 8 hours not to exceed 150 mg in 24 hours. Children 6 to under 12 years oral dosage is 12.5 mg every 4 hours or 25 mg every 8 hours not to exceed 75 mg in 24 hours. Children 2 to under 6 years oral dosage is 6.25 mg every 4 hours or 12.5 mg every 8 hours not to exceed 37.5 mg in 24 hours. For children under 2 years, there is no recommended dosage except under the advice and supervision of a physician.

(4) *Labeling.* The Panel recommends the Category I labeling for nasal decongestant active ingredients. (See part VIII. paragraph B. 1. below—Category I Labeling.)

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f. *Propylhexedrine (inhalant).* The Panel concludes that propylhexedrine (inhalant) is safe and effective as an inhalant nasal decongestant for OTC use as specified in the dosage section discussed below.

(1) *Safety.* Clinical experience has confirmed that propylhexedrine (inhalant) is safe in the dosage ranges used as a nasal decongestant. Because of a wide margin of safety and the relative freedom from toxic effects, use by inhalation is not contraindicated for patients in whom an ephedrine-like pressor or stimulant action would be undesirable (Ref. 1). Excessive doses, at least six inhalations per nostril, of propylhexedrine inhaler produced no undesirable side effects such as angina attacks, ECG changes, or vasopressor responses in 20 patients with history of severe angina pectoris due to arteriosclerosis (Ref. 2). Two inhalations of propylhexedrine inhaler, 250 mg per inhaler, is reported to deliver approximately 0.5 mg of the volatile amine to the nostril (Ref. 3).

Oral doses of propylhexedrine alone, 100 mg, in normal adults induces a 17 to 23 mm blood pressure rise and reflex bradycardia but no overt symptoms of euphoria, palpitation or dry mouth (Ref. 4). Another investigator reported that 250 mg by mouth induced only slight nervousness, anxiety and tachycardia (Ref. 5). A 3-year old who ingested 15 tablets of propylhexedrine, a total dose of 375 mg, developed pronounced symptoms of central nervous stimulation consisting of insomnia, tremor, muscular hypertonicity and tachycardia which subsided in 3 days (Ref. 6). Propylhexedrine is marketed outside of the United States as an anorexic.

One individual ingesting the contents of a propylhexedrine inhaler containing 250 mg of amine plus menthol and lavender oil, developed an extreme illness lasting 4 weeks and involved "shock lung" syndrome (Ref. 7). Two notes report psychotic behavioral changes in persons with a habit of chewing the inhaler or dissolving the contents in coffee and consuming it (Refs. 8, 9, and 10).

Rats inhaling propylhexedrine, 0.55–0.70 mg/800 ml air, for 6 to 10 minute periods daily for 30 days revealed no histological evidence of tracheobronchial mucosal irritation (Ref. 11). A double-blind study was undertaken to assess the effect of inhaler administration every 4 hours of propylhexedrine plus menthol vapors to 20 normal human volunteers and menthol vapors alone to 18 normal human volunteers over a 2-week period (Ref. 12). Nasal airway resistance measurements on days 1, 7 and 14 revealed no evidence of diminished responsiveness to the propylhexedrine inhaler with this repeated use. The results indicate that under these conditions of dosing, rebound congestion is not a prominent feature.

(2) *Effectiveness.* Four noncontrolled subjective evaluation studies of propylhexedrine inhaler in a total of 140 patients with various types of nasal congestion problems revealed subjective improvement with minimal side effects. Slight stinging occurred in some cases (Refs. 13 and 14). In one of these studies of 20 patients, the onset of subjective relief was noted between 30 seconds to 5 minutes following two inhalations per nostril with "clear nasal breathing" reported to persist for 30 to 120 minutes.

A recent well-controlled double-blind trial of adults with head colds has been done with inhalers containing either propylhexedrine plus menthol or menthol alone, and using single nostril airway resistance measurements (Ref. 15). Unfortunately, propylhexedrine alone was not used. However, menthol in an inhaler alone appeared to have no significant effect on nasal airway resistance but menthol plus propylhexedrine did significantly reduce nasal airway resistance for about 2 hours with a maximum effect at about 30 minutes. It should be noted that two inhalations were used in one nostril and then repeated after 2 hours. Measurements made 4 hours after the initial inhalation, that is, 2 hours after the repeat inhalation, suggest a possible rebound congestion.

A subsequent double-blind objective measurement study by another investigator compared the nasal decongestant effect of a propylhexedrine inhaler with a placebo inhaler in 50 adult patients with nasal congestion due to head cold, divided equally between active and placebo group (Ref. 16). Following a control period for recording baseline nasal airway resistance, each patient administered two inhalations per nostril from their coded inhaler. Nasal airway resistance (NAR) measured at intervals up to 4 hours demonstrated significant decrease in NAR in the propylhexedrine group compared to placebo for up to 90 minutes and decline toward control levels thereafter. These results were associated with patient perception of decreased nasal congestion during the first 90 minutes. In this single dose administration study no side effects or evidence of rebound congestion was noted.

(3) *Dosage.* Adults and children 6 to under 12 years inhalant dosage from an inhaler that shall deliver in each 800 ml of air 0.40 to 0.50 mg of propylhexedrine is 2 inhalations in each nostril not more frequently than every 2 hours. For children under 6 years, there is no recommended dosage except under the advice and supervision of a physician. The inhaler should retain effectiveness for a minimum of 2 to 3 months.

(4) *Labeling.* The Panel recommends the Category I labeling for nasal decongestant active ingredients. (See part VIII. paragraph B.1. below—Category I Labeling.)

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g. *Pseudoephedrine preparations (pseudoephedrine hydrochloride, pseudoephedrine sulfate) (oral).* The Panel concludes that the pseudoephedrine and its salts are safe and effective as oral nasal decongestants for OTC use as specified in the dosage section discussed below.

(1) *Safety.* Clinical experience has confirmed that pseudoephedrine and its salts (oral) are safe in the dosage ranges used as nasal decongestants. In a series of 21 patients who took 60 mg of pseudoephedrine orally, mild side effects such as drowsiness, insomnia, and headache occurred in six of these patients (Ref. 1).

In a study of cardiovascular effects, dose responses in four subjects showed that 210 to 240 mg or 3.0 to 3.4 mg/kg were required to raise diastolic blood pressure to 90 mm Hg or above (Ref. 2).

Acute blood pressure rises may occur, however, if pseudoephedrine in therapeutic doses is taken with MAO inhibitors (Refs. 3 and 4).

(2) *Effectiveness.* A double-blind subjective study in allergic rhinitis patients showed pseudoephedrine to be better than placebo (Ref. 1). In children, a double-blind subjective study showed pseudoephedrine to be better than placebo in allergic respiratory disease and possibly also in non-allergic respiratory conditions, but no statistics are given (Ref. 5). In a study of 88 patients, there were no differences between the drug and placebo group subjectively or by rhinometry (Ref. 6). However, significant increases in na-

sal flow rates up to 20 percent after 60 mg orally and lasting at least 2 hours have been shown in other series (Refs. 7 and 8). Recent work with measurements of nasal airway resistance confirms a nasal decongestant effect, after an oral dose of 60 mg lasting up to 4 hours and returning to control values by 6 hours (Ref. 9).

(3) *Dosage.* Adult oral dosage is 60 mg every 4 hours not to exceed a maximum of 360 mg in 24 hours. Children 6 to under 12 years oral dosage is 30 mg every 4 hours not to exceed 180 mg in 24 hours. Children 2 to under 6 years oral dosage is 15 mg every 4 hours not to exceed 90 mg in 24 hours. For children under 2 years, there is no recommended dosage except under the advice and supervision of a physician.

(4) *Labeling.* The Panel recommends the Category I labeling for nasal decongestant active ingredients. (See part VIII. paragraph B.1. below—Category I Labeling).

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h. *Xylometazoline hydrochloride (topical).* The Panel concludes that xylometazoline is safe and effective as a topical nasal decongestant for OTC use as specified in the dosage section discussed below.

(1) *Safety.* Clinical experience has confirmed that xylometazoline hydrochloride (topical) is safe in the dosage ranges used as a nasal decongestant. Because the decongestant effect of xylometazoline hydrochloride, administered as drops or sprays, persists up to 5 hours with gradual decline thereafter, objective measurement studies in adults revealed no rebound congestion after single administration of 0.05 or 0.1 percent solutions (Refs. 1 through 4). Both objective and subjective measurement studies of 0.05 percent xylometazoline in infants and 0.05 or 0.1 percent, in children, reveal negligible rebound congestion with 3 times daily dosing for periods of 2 days to 2 weeks (Refs. 5 through 9). No cardiovascular changes were produced by nasal application of xylometazoline (Refs. 5, 7, and 10). Because of these safety considerations, the Panel recommends that xylometazoline, which is currently a drug available only by prescription, be reclassified to permit OTC usage as well.

(2) *Effectiveness.* Objective measurement studies in acute and chronic rhinitis among adults showed a single application of xylometazoline, 0.1 percent drops or sprays, to induce a rapid (5 to 10 minutes) and a prolonged (up to 10 hours) decrease, in nasal airway resistance (Refs. 1 through 4). In infants and children, objective measurement studies (Ref. 5) and subjective evaluation (Refs. 7, 9, and 11) demonstrated the nasal decongestant effectiveness of 0.01, 0.05 and 0.1 percent xylometazoline drops or sprays.

(3) *Dosage.* Adult topical dosage is 2 to 3 drops or sprays in each nostril of a 0.1 percent aqueous solution every 8 to 10 hours. Children 2 to under 12 years topical dosage is 2 to 3 drops or sprays in each nostril of a 0.05 percent aqueous solution every 8 to 10 hours. Only drops should be used in children 2 to under 6 years since the spray is difficult to use in the small nostril. For children under 2 years, there is no recommended dosage except under the advice and supervision of a physician.

(4) *Labeling.* The Panel recommends the Category I labeling for nasal decongestant active ingredients. (See part VIII. paragraph B.1. below—Category I Labeling.) In addition, the Panel recommends the following specific labeling: *Warnings:* (i) *For products containing a concentration of 0.05 percent xylometazoline hydrochloride:* "Do not give this product to children under 2 years except under the advice and supervision of a physician".

(ii) *For products containing a concentration of 0.1 percent xylometazoline hydrochloride:* "For adult use only. Do not give this product to children under 12 years except under the advice and supervision of a physician".

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Category I Labeling

The Panel recommends the following Category I labeling for nasal decongestant active ingredients to be generally recognized as safe and effective and not misbranded as well as the specific labeling discussed in the individual ingredient statements:

a. *Indications.* (1) "For temporary relief of nasal congestion due to the common cold".

(2) "For temporary relief of nasal congestion due to hay fever or other upper respiratory allergies".

(3) "For temporary relief of nasal congestion associated with sinusitus".

(4) "For the temporary relief of stuffy nose (stopped up nose, nasal stuffiness, clogged up nose)".

(5) "Reduce swelling of nasal passages; shrinks swollen membranes".

(6) "Decongests nasal passages".

(7) "Temporarily restores freer breathing through the nose".

(8) "Helps clear nasal passages".

(9) "Helps decongest sinus openings, sinus passages".

(10) "Promotes nasal and/or sinus drainage".

(11) For products with claims for duration of effect: Statements as to duration of effect must be substantiated and

accompanied by a specific time period expressed in minutes or hours, as appropriate.

(12) For products used as topical nasal decongestants with claims for rapid onset of action: Statements relating to time to onset of action, such as, "fast" or "quick", must be accompanied by a specific time period expressed in minutes.

(13) For topical nasal decongestants which can demonstrate a cooling sensation: (i) "Provides cooling sensation".

(ii) "Cooling".

(iii) "Cools nasal passages".

b. *Warnings.* (1) *For products used as topical nasal decongestants:* (i) "Do n t exceed recommended dosage because symptoms may occur such as burning, stinging, sneezing, or increase of nasal discharge".

(ii) "Do not use this product for more than 3 days. If symptoms persist, consult a physician".

(iii) "The use of this dispenser by more than one person may spread infection".

(2) *For products used as oral nasal decongestants:* (i) "Do not exceed recommended dosage because at higher doses nervousness, dizziness, or sleeplessness may occur".

(ii) "If symptoms do not improve within 7 days or are accompanied by high fever, consult a physician before continuing use".

(iii) "Do not take this product if you have high blood pressure, heart disease, diabetes or thyroid disease except under the advice and supervision of a physician.

(iv) *"Drug interaction precaution:* Do not take this product if you are presently taking a prescription antihypertensive or antidepressant drug containing a monoamine oxidase inhibitor except under the advice and supervision of a physician".

(3) *For products used as inhalant nasal decongestants:* (i) "This inhaler should be warmed in the hand before use to increase effectiveness".

(ii) "Do not give this product to children under 6 years except under the advice and supervision of a physician".

(iii) "Children should not have unsupervised access to this inhaler".

(iv) *"Caution:* Not for use by mouth".

2. *Category II conditions under which nasal decongestant ingredients are not generally recognized as safe and effective or are misbranded.* The use of nasal decongestants under the following conditions is unsupported by scientific data, and in some instances by sound theoretical reasoning. The Panel concludes that the following active ingredients and labeling should be removed from the market until scientific testing supports its use.

Category II Active Ingredients

The Panel has classified the following nasal decongestant active ingredients as not generally recognized as safe and effective or as misbranded:

Mustard oil (allylisothiocyanate) (topical/inhalant)

Turpentine oil (spirits of turpentine) (oral)

a. *Mustard oil (allylisothiocyanate) (topical/inhalant).* The Panel concludes that mustard oil is neither safe nor effective for topical or inhalant OTC use as a nasal decongestant.

(1) *Safety.* Mustard oil is obtained from Black mustard. Black mustard, which is official in the National Formulary XI, consists of dried, ripe seeds from various varieties of either or both of two species of the genus *Brassica* (*Cruciferae*), namely, *Brassica nigra* (Brown mustard) and *Brassica juncea* (Chinese mustard) (Ref. 1). The formation of the irritant constituent, allylisothiocyanate (active ingredient), in black mustard seed results from the hydrolytic activity of the enzyme mirosin, on a glycoside substrate sinigrin (potassium mironate). Allylisothiocyanate is designated as the volatile oil of mustard (Ref. 1), as opposed to the fixed (expressed) oil of mustard, which is composed chiefly of the glycerides of oleic, arachidic, and other fatty acids (Ref. 2). Allylisothiocyanate, the volatile oil of mustard, is isolated from black mustard by distillation (Ref. 3).

The active ingredient of mustard oil, allylisothiocyanate, is present in about 0.6 percent concentration in mustard seed powder. Mustard powder, because of this substance, is a local irritant which has been used in topically applied preparations, e.g., "mustard plaster," for its rubefacient and counterirritant effects and by oral administration for its emetic effect. The vapors of mustard oil are reported to cause irritation of conjunctival, nasal and bronchial mucosa (Refs. 4, 5, and 6). A 15 percent solution of mustard oil in liquid petrolatum has been used to induce mucosal inflammation in an experimental protocol to study anti-inflammatory agents (Refs. 4 and 7).

The Panel is unable to determine a safe dose for mustard oil for topical use or as an inhalant that is also effective as a nasal decongestant.

(2) *Effectiveness.* The effectiveness of mustard oil as a nasal decongestant is uncertain. Black mustard has been used for centuries as a rubefacient and a counterirritant. Mustard plaster, a poultice type of medicament, is used for relieving the pain resulting from bruises and sprains. Mustard preparations are commonly used internally as emetics and as food condiments (Ref. 1). The usual emetic dose of black mustard is 10 gm (Ref. 8).

There is no evidence to support the effectiveness of mustard oil (allylisothiocyanate) as a nasal decongestant when applied topically or used as an inhalant. The Panel is aware that the official preparation Mustard Plaster, National Formulary XI, is indicated for use as a local irritant. The Panel is also aware of a marketed product containing mustard oil in combination with other volatile oils for OTC use. The product is administered by inhalation from the cork that seals the OTC medicine vial (Ref. 9). There is no evidence in the literature that this oil or its active ingredient, allylisothiocyanate, possesses nasal decongestant properties. Literature sources all refer to the local irritant effect only (Refs. 4, 5, 8, and 9).

(3) *Evaluation.* The Panel is unable to determine a safe topical or inhalant dosage for mustard oil for use as a nasal decongestant. The Panel is of the opinion that the risk from topical or inhalant administration outweighs whatever benefit might occur. Therefore, the Panel concludes that mustard oil is not safe for topical or inhalant use as a nasal decongestant.

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b. *Turpentine oil (spirits of turpentine) (oral).* The Panel concludes that oil of turpentine is not safe for OTC use when taken orally as a nasal decongestant.

(1) *Safety.* Oil of turpentine is a volatile oil distilled from turpentine, an oleoresin obtained from the pine tree. It has a characteristic odor and taste. The substance has been administered orally, topically, and by inhalation.

In doses of 15 ml in children and 150 ml in adults, fatal poisoning may occur (Ref. 1). Excessive oral doses produce marked irritation of the alimentary tract, especially of the stomach and of the pelvic organs. Toxic symptoms include vomiting, diarrhea, acute pain, renal irritation, bloody stools and hyperemia of all abdominal organs. Continued use may lead to cloudy swelling and fatty degeneration of the liver. Abnormal central nervous system symptoms may develop (Refs. 2 and 3).

Since no safe oral dose has been established for effective use as a nasal decongestant, the Panel concludes that turpentine oil should not be available for oral OTC use as a nasal decongestant. However, elsewhere in this document, the Panel concludes that the ingredient is safe when applied topically or used as

an inhalant but that there are insufficient data to permit final classification of its effectiveness for inhalant or topical use as a nasal decongestant. (See part VIII. paragraph B.3.m. below—Turpentine oil (spirits of turpentine) (topical/inhalant).)

(2) *Effectiveness.* Oil of turpentine is irritating and its chief suggested uses are based on this property (Refs. 1 and 4). There is no evidence to support its effectiveness as a nasal decongestant when taken orally.

(3) *Evaluation.* The Panel is unable to determine a safe oral dosage for turpentine oil for use as a nasal decongestant. The Panel is of the opinion that the risk from oral administration outweighs whatever benefit might occur. Therefore, the Panel concludes that turpentine oil is not safe for oral use as a nasal decongestant.

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Category II Labeling

All claims that state or imply a therapeutic action or safety property peculiar to the preparation that cannot be demonstrated in controlled studies are not acceptable. The Panel has previously discussed such labeling. (See part II. paragraph O. above—CCABA Product Labeling Claims Not Supported by Scientific Evidence.) However, labeling that is descriptive of the product such as its taste or appearance are acceptable.

The Panel concludes that the examples of language expressed in the following misleading claims are excessive and claims either too much or claims effects which do not occur and therefore such labeling should be removed from the market until scientific testing supports their use:

a. *Topical nasal decongestants.* (1) Reference to "germ-laden mucous" is unacceptable because it implies a curative action rather than symptom-relieving.

(2) The statement "Seldom causes rebound distress like others" is unacceptable because Category I topical nasal decongestants if used in accordance with labeled instructions as to dose and frequency should seldom cause rebound distress.

(3) The term "nonirritating base" is unacceptable because it may encourage a misleading conclusion about the safety characteristics of the total product.

b. *Oral nasal decongestants.* (1) The statement "Mild stimulant to overcome drowsiness", is unacceptable because there is no evidence to prove that an OTC decongestant could overcome drowsiness caused by antihistamine.

(2) Reference to "fast" or "prompt" onset of relief is unacceptable for oral products because this action does not occur and is a claim allowed only for topical products.

c. *Topical or oral nasal decongestants.* (1) Reference to effect on "local congestion" is unacceptable since this may be confused with congestion in the bronchioles and chest.

(2) Reference to "extra strength", the "most effective", "improved remedy" are unacceptable because they suggest the product is particularly effective. All Category I ingredients have been judged effective but no acceptable controlled studies were submitted to the Panel documenting one preparation as more effective than another.

(3) Reference to "used by" or "most recommended by doctors or scientists" is unacceptable because it is difficult to substantiate.

(4) "Checks irritation caused by cold virus" is unacceptable because it implies a curative action rather than symptom-relieving.

3. *Category III conditions for which the available data are insufficient to permit final classification at this time.* The Panel concludes adequate and reliable scientific evidence is not available at this time to permit final classification of the claimed ingredients and conditions listed below. The Panel believes it reasonable to provide 3 years for the development and review of such evidence. Marketing need not cease during this time if adequate testing is undertaken. If adequate effectiveness data are not obtained within 3 years, however, the conditions listed in this category should no longer be marketed in over-the-counter nasal decongestant products. Effectiveness as a nasal decongestant must be demonstrated by determining the ability of a drug to reduce nasal obstruction in patients with acute or chronic rhinitis.

Category III Active Ingredients

The Panel concludes that the available data are insufficient to permit final classification of the following claimed nasal decongestant active ingredients:

Beechwood creosote
Bornyl acetate (topical)
Camphor (topical/inhalant)
Cedar leaf oil (topical)
1-Desoxyephedrine (inhalant)
Ephedrine preparations (oral): Ephedrine, Ephedrine hydrochloride, Ephedrine sulfate, Racephedrine hydrochloride
Eucalyptol/eucalyptus oil (topical/inhalant)
Menthol/peppermint oil (topical/inhalant)
Phenylpropanolamine hydrochloride (topical)
Thenyldiamine hydrochloride (topical)
Thymol (inhalant)
Turpentine oil (spirits of turpentine) (topical/inhalant)

a. *Beechwood creosote.* The Panel concludes that beechwood creosote is safe in the dosage ranges used as a nasal decongestant but there are insufficient data to permit final classification of its effectiveness for OTC use as a nasal decongestant.

(1) *Safety.* Clinical experience has confirmed that beechwood creosote in the usual dosages contained in lozenges or cough mixtures for nasal decongestant activity is safe.

Creosote is a distillate of wood tar and has a smoky color and a pungent taste. Dosages in excess of 4 gm 3 times daily produces giddiness, dimness of vision, circulatory collapse, convulsions and coma (Ref. 1). Because of the taste, it is normally given well-diluted (Ref. 2). Occasional adverse gastrointestinal side effects are mentioned in one report but are poorly documented (Ref. 3). Based on the available data and the presence of beechwood creosote on the market for many years, the Panel concludes that this ingredient is safe for OTC use.

(2) *Effectiveness.* Except for a recent submission (Ref. 4), there have been no well-controlled studies documenting the effectiveness of beechwood creosote alone or in combination as a nasal decongestant. A single study is reported dealing with nasal airway resistance in 66 patients with degrees of the "common cold." These patients were studied by objective techniques and this study showed significant reduction in nasal resistance for beechwood creosote combination as compared with a placebo 2 hours following administration. Subjective studies with respect to runny nose should note significant changes from the placebo. It is stated that the investigator global evaluations were too small in number to permit statistical interpretation. In reviewing this study it is difficult for the Panel to interpret these statistical analyses which appear to be cumbersome and confusing. In addition, since no dosage information is supplied, the Panel questions the acceptability of the study.

According to the standard compendia (Refs. 1 and 5), an average dosage of beechwood creosote is 250 mg 3 or 4 times daily. In the two submissions to the Panel listing creosote, the dosages are 3.29 mg/lozenge and 33 mg/15 ml every 3 hours (Refs. 6). This 40- to 80-fold difference in dose (3.29 mg/lozenge, 8 doses/day) appears illogical and there is no evidence to indicate that creosote is effective in such low doses. The Panel concludes that further studies are needed to determine effectiveness.

(3) *Proposed dosage.* Adult oral dosage is 250 mg every 4 to 6 hours not to exceed 1500 mg in 24 hours. Children 6 to under 12 years oral dosage is 125 mg every 4 to 6 hours not to exceed 750 mg in 24 hours. Children 2 to under 6 years oral dosage is 62.5 mg every 4 to 6 hours not to exceed 375 mg in 24 hours. For children under 2 years, there is no recommended dosage except under the advice and supervision of a physician.

(4) *Labeling.* The Panel recommends the Category I labeling for nasal decongestant active ingredients. (See part IV. paragraph B.1. above—Category I Labeling).

(5) *Evaluation.* Data to demonstrate effectiveness as a nasal decongestant will be required in accordance with the guidelines set forth below for testing nasal decongestant drugs. (See part IV. para-

graph C. below—Data Required for Evaluation.)

REFERENCES

(1) "The United States Dispensatory and Physicians' Pharmacology," 26th Ed., Edited by Osol, A., R. Pratt and M. D. Altschule, J. B. Lippincott Co., Philadelphia, p. 341, 1967.

(2) "Drill's Pharmacology in Medicine," 2d Ed., Edited by DiPalma, J. R., McGraw-Hill Co., New York, p. 690, 1958.

(3) Stevens, M. E., A. K. Ronan, T. S. Sourkes and E. M. Boyd, "On the Expectorant Action of Creosote and the Guaiacols," *Canadian Medical Association Journal*, 48:124–127, 1943.

(4) OTC Volume 040289.

(5) "The National Formulary," 7th Ed., American Pharmaceutical Association, Washington, D.C., pp. 105–106, 1942.

(6) OTC Volume 040208 and 040235.

b. *Bornyl acetate (topical)*. The Panel concludes that bornyl acetate is safe in the dose ranges used when applied topically but there are insufficient data to permit final classification of its effectiveness for topical OTC use as a nasal decongestant.

(1) *Safety*. Clinical experience has apparently confirmed that bornyl acetate (topical) is safe in the dosage ranges used as a nasal decongestant. There are no studies to substantiate its safety. The Merck Index (Ref. 1) states that this compound may cause nausea and vomiting, mental confusion, dizziness and convulsions. The dose is not given. The amount present in a commercially available inhaler is not given (Ref. 2). It is one of several aromatic substances in the inhaler.

(2) *Effectiveness*. There are no well-controlled studies documenting the effectiveness of bornyl acetate (topical) as a nasal decongestant. In a report (Ref. 3), bornyl acetate was one of eleven aromatic substances evaluated as nasal decongestants. Patients presumably with nasal congestion were used. Nasal resistance was measured before treatment and at 5, 15, 30, 60, 90 and 120 minutes after treatment. Bornyl acetate 112.5 mg was impregnated on a cotton wick through which air was forced and the patient inhaled. In the morning, 50 cc of air was administered in each nostril and 150 cc in each nostril in the afternoon. In 11 patients, there was a statistically significant decrease in the nasal resistance at the higher dose. This was not a well designed study.

(3) *Proposed dosage*. The Panel is unable to determine a proposed dosage. The Panel concludes that the pharmaceutical industry should consult with the Food and Drug Administration as to a suitable proposed dosage for testing. Otherwise, the Panel recommends that each drug manufacturer evaluate the dosage as labeled on the manufacturer's marketed product(s).

(4) *Labeling*. The Panel recommends the Category I labeling for nasal decongestant active ingredients. (See part VIII. paragraph B.1. above—Category I Labeling.)

(5) *Evaluation*. Data to demonstrate effectiveness will be required in accordance with the guidelines set forth below for nasal decongestant drugs. (See part VIII. paragraph C. below—Data Required for Evaluation.)

REFERENCES

(1) "The Merck Index," 8th Ed., Merck and Company, Inc., Rahway, New Jersey, p. 160, 1968.

(2) OTC Volume 040065.

(3) Grubb, T. C., "The Nasal Decongestant Effect of Aromatic Substances," Draft of unpublished study is included in OTC Volume 040298.

c. *Camphor (topical/inhalant)*. The Panel concludes that camphor is safe in the dosage ranges used when applied topically or as an inhalant but there are insufficient data to permit final classification of its effectiveness for topical/inhalant OTC use as a nasal decongestant.

(1) *Safety*. Clinical experience has confirmed that camphor (tropical/inhalant) is safe in the dosage ranges used as a nasal decongestant.

Camphor is a local irritant producing skin redness when rubbed on the skin. However, when not vigorously applied, it may produce a feeling of coolness on the skin as does menthol. It acts similarly on the respiratory tract. Taken orally in small doses it produces a feeling of warmth and comfort in the stomach but in larger doses it is irritating and can cause nausea and vomiting. Camphor also has a mild local anesthetic action and its application to the skin may be followed by numbness. The systemic effects are primarily related to stimulation of the central nervous system. The ingestion of solid camphor by children can cause convulsions (Ref. 1). As little as 0.75 gm of camphor equivalent to a teaspoonful of linament of camphor or camphorated oil which contains 20 percent camphor has been fatal to a child. Commercially available ointments containing mixtures of volatile substances for use as decongestants or antitussives contain about 5 percent camphor. Since it is conceivable that ingestion of a sufficient amount of such a preparation could produce toxic effects in a young child, a suitable warning should be present on the label. The ingestion of 2 gm of camphor generally produces toxic effects in an adult although up to 1.5 oz has been ingested with recovery (Ref. 2).

(2) *Effectiveness*. There are no well-controlled studies documenting the effectiveness of camphor (topical/inhalant) as a nasal decongestant. Its effectiveness is uncertain due to lack of properly controlled studies of the substance by itself.

Using an electronic technique for measuring nasal airflow in infants and children, Noller reported that following application of a camphor-containing ointment to the nasal passageway resulted in an initial reduction in airflow followed by an increase in airflow over the pretreatment level. The study report did not, however, indicate the concentration of camphor applied nor were data supplied in the report (Ref. 3). Other studies involving the objective measurement of the nasal decongestant activity of camphor utilized mixtures of volatile substances in topically applied ointments (Refs. 4 through 6) and in steam inhalations (Ref. 7). In these studies, although significant nasal decongestion compared to placebo has been demonstrated, it is not evident whether the camphor component contributed to this effect.

(3) *Proposed dosage*. Dosage for adults and children 2 to under 12 years is as follows: (i) For topical use as a 5 percent ointment preparation: To be rubbed on the throat, chest and back as a thick layer. The area of application may be covered. However, clothing should be left loose about the throat and chest to help the vapor rise to reach the nose and mouth. Applications may be repeated up to 3 times daily.

(ii) For steam inhalation use as a 7 percent solution: 1 tablespoonful of solution per quart of water is added directly to the water in any hot steam vaporizer, bowl or washbasin; or 2 teaspoonfuls of solution per pint of water are added to an open container of boiling water. Breathe in vapors during the period of medicated steam generation. May be repeated 3 times daily.

(iii) For topical use as a lozenge 0.2 to 15 mg: Allow lozenge to dissolve slowly in mouth. May be repeated every ½ to 1 hour.

For children under 2 years, there is no recommended topical or inhalant dosage except under the advice and supervision of a physician.

(4) *Labeling*. The Panel recommends the Category I labeling for topical nasal decongestant active ingredients. (See part VIII. paragraph B.1. above—Category I Labeling.) In addition, the Panel recommends the following specific labeling: (i) For topical ointment use: Warning "For external use only. Do not take by mouth or place in nostrils".

(ii) For steam inhalation use: Warning: "For steam inhalation only. Do not take by mouth".

(5) *Evaluation*. The Panel made the following recommendations: (i) For topical ointment use: Data to demonstrate effectiveness will be required in accordance with the guidelines set forth below for testing nasal decongestant drugs. (See part VIII. paragraph C. below—Data Required for Evaluation.)

(ii) For steam inhalation use: Data to demonstrate effectiveness will be required in accordance with the guidelines set forth below for testing nasal decongestant drugs. (See part VIII. paragraph C. below—Data Required for Evaluation).

(iii) For topical use as a lozenge: Data to demonstrate effectiveness will be required in accordance with the guidelines set forth below for testing nasal decongestant drugs. (See part VIII. paragraph C. below—Data Required for Evaluation).

REFERENCES

(1) Swinyard, E. A. "Demulcents, Emollients, Protectives and Absorbents, Antiperspirants and Deodorants, Absorbable Hemostatics, Astringents, Irritants, Sclerosing Agents, Caustics, Keratolytics, Antiseborrheics, Melanizing and Demelanizing Agents, Mucolytics, and Certain Enzymes," in "The Pharmacological Basis of Therapeutics," 4th Ed., Edited by Goodman, L. S. and A. Gilman,

The MacMillan Co., New York, p. 993, 1970.

(2) Thienes, C. H. and T. J. Haley, "Clinical Toxicology of Commercial Products," 3d Ed., Lea and Febiger, Philadelphia, pp. 24–25, 1955.

(3) Noller, H. G., "Electronic Measurements on the Nasal Mucous Membrane During Exposure to Menthol," (English translation), ("Elektronische Messungen an der Nasenschleimhaut unter Methol-wirkung"), *in* "Menthol and Menthol-containing External Remedies," Edited by Dost, F. H. and B. Leiber, Georg Thieme Verlag, Stuttgart, Germany, pp. 146–153, 1966.

(4) Blanchard, C. L., S. J. Borsanyi and T. C. Grubb, "Evaluation of Nasal Decongestant Drugs," *The Eye, Ear, Nose and Throat Monthly*, 43:76–82, 1964.

(5) Stamos, E., "Vaporub. Nasal Decongestant Study: Vick Rhinorrheometer. CRD 71–1," Draft of unpublished data is included in OTC Volume 040298.

(6) Carter, V. H., "Vaporub. Nasal Decongestant Study: Vick Rhinorrheometer. CRD 72–7," Draft of unpublished data is included in OTC Volume 040298.

(7) Ciampi, L. A., "Vaposteam. Nasal Decongestant Vick Rhinorrheometer. CRD 71–5," Draft of unpublished data is included in OTC Volume 040298.

d. *Cedar leaf oil (topical)*. The Panel concludes that cedar leaf oil is safe in the dosage ranges used when applied topically but there are insufficient data to permit final classification of its effectiveness for topical OTC use as a nasal decongestant.

(1) *Safety*. Clinical experience has confirmed that cedar leaf oil (topical) is safe in the dosage ranges used as a nasal decongestant.

Cedar leaf oil is the volatile oil steam distilled from the fresh leaves of Thuja occidentialis. The oil is reputed to be ecbolic but abortions cannot be induced with safe doses. The actions are like turpentine but the toxicity greater. In most cases oral ingestion of a teaspoonful may cause illness in an adult and less than 1 oz may be lethal (Refs. 1 and 2).

Several studies support the safety of a topically applied mixture of volatile oils, 16 percent weight/weight, in petrolatum. Although this mixture contains cedar leaf oil, the concentration of individual ingredients is not specified (Ref. 3).

(2) *Effectiveness*. There are no well-controlled studies documenting the effectiveness of cedar leaf oil (topical) as a nasal decongestant. Cedar leaf oil by inhalation is probably transiently effective as a nasal decongestant.

In a study of 10 patients with head colds, not double-blind or placebo-controlled, inhalation of a measured volume of cedar leaf oil vapors induced a significant nasal decongestant effect persisting for 30 minutes as measured by anterior rhinometry. Increasing the volume of inhaled vapors intensified but did not prolong the decrease in nasal resistance (Ref. 4).

In a placebo-controlled crossover study of 36 patients with head colds, application to the chest of a 16 percent weight/weight mixture of volatile oils in petrolatum containing cedar leaf oil demonstrated an apparently significant decrease in nasal resistance compared to the petrolatum control over a 4 hour observation period. The concentration of the cedar leaf oil was not specified. A similar study in 20 additional patients resulted in control and treatment data with overlapping standard errors (Ref. 4). Other studies involving the objective measurements of the nasal decongestant activity of cedar leaf oil utilized mixtures of volatile substances in topically applied ointments (Refs. 5 through 7) and in steam inhalations (Ref. 8). In these studies, although significant nasal decongestion compared to placebo was demonstrated, it was not evident whether the cedar leaf oil component contributed to this effect.

(3) *Proposed dosage*. The Panel is unable to determine a proposed dosage. The Panel concludes that the pharmaceutical industry should consult with the Food and Drug Administration as to a suitable proposed dosage for testing. Otherwise, the Panel recommends that each drug manufacturer evaluate the dosage as labeled on the manufacturer's marketed product(s).

(4) *Labeling*. The Panel recommends the Category I labeling for nasal decongestant active ingredients. (See part VIII. paragraph B.1. above—Category I Labeling).

(5) *Evaluation*. Data to demonstrate effectiveness will be required in accordance with the guidelines set forth below for nasal decongestant drugs. (See part VIII. paragraph C. below—Data Required for Evaluation).

REFERENCES

(1) "Clinical Toxicology of Commercial Products. Acute Poisoning," 3d Ed., Edited by Gleason, M. N., R. E. Gosselin, H. C. Hodge and R. P. Smith, The Williams and Wilkins Co., Baltimore, p. 65, 1969.

(2) "The Dispensatory of the United States of America," 25th Ed., Edited by Osol, A. and G. E. Farrar, Jr., J. B. Lippincott, Philadelphia, p. 1901, 1960.

(3) OTC Volume 040057.

(4) Grubb, T. C., "The Nasal Decongestant Effect of Aromatic Substances," Draft of unpublished study is included in OTC Volume 040298.

(5) Blanchard, C. L., S. J. Borsany and T. C. Grubb, "Evaluation of Nasal Decongestant Drugs," *The Eye, Ear, Nose and Throat Monthly*, 43:76–82, 1964.

(6) Stamos, E., "Vaporub. Nasal Decongestant Study: Vick Rhinorrheometer. CRD 71–1" Draft of unpublished data included in OTC Volume 040298.

(7) Carter, V. H., "Vaporub. Nasal Decongestant Study: Vick Rhinorrheometer. CRD 72–7," Draft of unpublished data is included in OTC Volume 040298.

(8) Ciampi, L. A., "Vaposteam. Nasal Decongestant Vick Rhinorrheometer. CRD 71–4," Draft of unpublished data is included in OTC Volume 040298.

e. *1-Desoxyephedrine (inhalant)*. The Panel concludes that 1-desoxyephedrine is safe in dosage ranges used when used as an inhalant but there are insufficient data to permit final classification of its effectiveness for inhalant OTC use as a nasal decongestant.

(1) *Safety*. Clinical experience has confirmed that 1-desoxyephedrine (inhalant) is safe in the dosage ranges used as a nasal decongestant.

Aqueous nose drops and aqueous spray in concentrations up to 1 percent caused burning, stinging, rhinorrhea and sneezing in up to 21.5 percent of subjects. Palpitations were rare (Ref. 1). With oral doses of 50 to 100 mg two of ten subjects had transient dizziness and nervousness but no blood pressure changes were seen (Ref. 2). No untoward effects of an oral dose of 25 mg 3 times daily for up to 28 days were observed in eight patients (Ref. 2).

(2) *Effectiveness*. There are no well-controlled studies documenting the effectiveness of 1-desoxyephedrine as a nasal decongestant. The effectiveness is therefore uncertain, as data are conflicting and properly controlled objective studies have not been presented.

Uncontrolled studies using nasal drops, 0.25 percent to 1.0 percent concentration, suggest that nasal mucous membrane constriction does occur at the higher concentrations (Ref. 1). An uncontrolled subjective study using an inhaler in 100 patients showed relief of nasal obstruction in 89 percent of cases. Onset of relief was usually in 1 minute and lasted up to 4 hours (Ref. 3). In another similar study duration of relief varied from ½ to 2 hours (Ref. 4). Two double-blind studies of inhalers containing aromatic oils with and without 1-desoxyephedrine showed no differences in nasal airflow studies using the Butler-Ivy technique (Refs. 5 and 6). However, one study (Ref. 6) showed that the inhalers with or without 1-desoxyephedrine were more effective than a placebo inhaler. This suggests the possibility that at least part of the effectiveness of the inhaler might be due to the aromatic oils. Some improvement for less than 30 minutes in airway resistance was shown for camphor, menthol, and bornyl acetate (Ref. 7).

Two single-blind studies comparing an inhaler containing aromatic oils and 1-desoxyephedrine, an inhaler containing only 1-desoxyephedrine, and a placebo inhaler were done using nasal airway resistance measured by a rhinorrheometer (Refs. 8 and 9). Both studies showed that the inhaler with aromatic oils and 1-desoxyephedrine was better than the inhaler containing only 1-desoxyephedrine and both were better than the placebo. Activity was maintained for at least 30 minutes with a maximum at 5 minutes but for less than 60 minutes. These studies suggest that 1-desoxyephedrine has some transient nasal vasoconstrictor effect.

In a recent double-blind, noncrossover, subjective rhinoscopic study of 100 male patients both the drug containing inhaler and placebo inhaler gave significant subjective effect for up to 60 minutes (Ref. 10). Slight rhinoscopic improvement was present in both groups. However, the drug containing inhaler groups, when compared with placebo had significantly greater subjective relief and greater improvement in rhinoscopic parameters.

The above review suggests that 1-desoxyephedrine probably has a nasal vasoconstrictor effect which is relatively brief. However, to be certain of effectiveness, double-blind studies with objective measurements of nasal airway resistance are required. These studies should also provide information as to rebound congestion with repeated nasal use.

(3) *Proposed dosage.* Adult inhalant dosage from an inhaler that shall deliver in each 800 ml air 40 to 150 mcgm l-desoxyephedrine is 2 inhalations in each nostril not more frequently than every 2 hours. Children 6 to under 12 years inhalant dosage from an inhaler that shall deliver in each 800 ml air 40 to 150 mcgm l-desoxyephedrine is 1 inhalation in each nostril not more frequently than every 2 hours. For children under 6 years, there is no recommended dosage except under the advice and supervision of a physician.

(4) *Labeling.* The Panel recommends the Category I labeling for nasal decongestant active ingredients (See part VIII. paragraph B.1. above—Category I Labeling.)

(5) *Evaluation.* Data to demonstrate effectiveness will be required from one additional objective nasal airway resistance study in patients with nasal congestion due to acute rhinitis in accordance with the guidelines set forth below for nasal decongestant drugs. (See part VIII. paragraph C. below—Data Required for Evaluation.)

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(1) Fabricant, N. D. et al., "Clinical Evaluation," Draft of unpublished data is included in OTC Volume 040298.

(2) Batterman, R. C., "Studies with Levodesoxyephedrine," Draft of unpublished data is included in OTC Volume 040298.

(3) Greenberg, L., "Resume of Clinical Study of 1-Desoxyephedrine Inhaler," Draft of unpublished data is included in OTC Volume 040298.

(4) Memo to Moore, H. L. from J. S. Scanlan, "Improved Inhaler," is included in OTC Volume 040298.

(5) Memo to Scanlan, J. S. from W. E. Burke, "Current Domestic Inhaler—Clinical Evaluation," is included in OTC Volume 040298.

(6) Sanford, T., "Inhaler," Draft of unpublished data is included in OTC Volume 040298.

(7) Grubb, T. C., "The Nasal Decongestant Effect of Aromatic Substances," Draft of unpublished data is included in OTC Volume 040298.

(8) Mendoza, J. A., "Vick Inhaler," Draft of unpublished data is included in OTC Volume 040298.

(9) Turgeon, R. F., "Vick Inhaler," Draft of unpublished data is included in OTC Volume 040298.

(10) OTC Volume 040231.

f. Ephedrine preparations (ephedrine, ephedrine hydrochloride, ephedrine sulfate, racephedrine hydrochloride) (oral). The Panel concludes that ephedrine and its salts are safe in the dosage ranges used orally but there are insufficient data to permit final classification of their effectiveness for oral OTC use as nasal decongestants.

(1) *Safety.* Clinical experience has confirmed that ephedrine and its salts (oral) are safe in the dosage ranges used as a nasal decongestant.

Ephedrine has both central and peripheral effects when absorbed systemically and stimulates, directly or indirectly, both alpha and beta receptors (Ref. 1). In clinical usage the central effects are stimulatory and include tenseness, nervousness, tremor and sleeplessness. Peripheral effects include bronchodilation, and possible shrinkage of mucous membranes (decongestion) although this has not been documented. Other peripheral effects include awareness of heartbeat and tachycardia accompanied usually by some elevation of blood pressure, both systolic and diastolic. The cardiovascular and central effects set limits on dosage, limits which vary widely among patients as judged by clinical experience. Anorexia and nausea also occur in some patients. Difficulty in urination may occur in older males with prostatic hypertrophy. Overdosage results in exaggeration of the side effects which patients describe as disagreeable and can usually be depended upon to prevent overuse or abuse. Ordinary doses may cause marked and potentially dangerous increases in blood pressure in patients taking monoamine oxidase (MAO) inhibitors.

(2) *Effectiveness.* There are insufficient studies documenting the effectiveness of ephedrine and its salts (oral) as nasal decongestants. One controlled objective measurement study in patients with nasal obstruction demonstrated nasal decongestant effectiveness of orally administered ephedrine sulfate in doses of 25 mg (Ref. 2). No conclusive data were found to support claims of effectiveness for doses 8 to 12 mg contained in OTC submissions.

(3) *Proposed dosage.* Adult oral dosage is 8 to 12 mg not more than every 4 hours not to exceed 72 mg in 24 hours. Children 6 to under 12 years oral dosage is 4 to 6 mg not more than every 4 hours not to exceed 36 mg in 24 hours. Children 2 to under 6 years oral dosage is 2 to 3 mg not more than every 4 hours not to exceed 18 mg in 24 hours. For children under 2 years, there is no recommended dosage except under the advice and supervision of a physician.

(4) *Labeling.* The Panel recommends the Category I labeling for nasal decongestant active ingredients. (See part VIII. paragraph B.1. above—Category I Labeling.)

(5) *Evaluation.* Data to demonstrate effectiveness will be required in accordance with the guidelines set forth below for nasal decongestant drugs. (See part VIII. paragraph C. below—Data Required for Evaluation.)

REFERENCES

(1) "The Pharmacological Basis of Therapeutics," 3d Ed., Edited by Goodman, L. S. and A. Gilman, The MacMillan Co., New York, pp. 505–506, 1965.

(2) McLaurin, J. W., W. F. Shipman and R. Rosedale, "Oral Decongestants," *Laryngoscope*, 71:56–67, 1961.

g. Eucalyptol/eucalyptus oil (topical/inhalant). The Panel concludes that eucalyptol/eucalyptus oil is safe in the dosage ranges used when applied topically or as an inhalant but there are insufficient data to permit final classification of its effectiveness for topical or inhalant OTC use as a nasal decongestant.

(1) *Safety.* Clinical experience has confirmed that eucalyptol/eucalyptus oil (topical/inhalant) is safe in the dosage ranges used as a nasal decongestant.

Eucalyptus oil is about 70 percent active eucalyptol. Fatalities have followed doses of the oil as small as 3.5 ml although recovery has occurred after doses of 20 and even 30 ml. Symptoms include epigastric burning with nausea and vomiting, vertigo, ataxia, muscle weakness and stupor (Refs. 1 and 2). A study of 223 subjects in which an ointment containing several volatile substances including eucalyptus oil 1.3 percent was applied for 48 hours to both areas of intact skin under a patch and to abraded skin revealed no instances of irritation, inflammation, wheal or hives following the period of exposure (Ref. 3). A study of 10 subjects who received application of an ointment containing several volatile substances including eucalyptus oil 1.3 percent to their trunks 3 times daily for 3 weeks, then 1 week off followed by another 1 week of treatment, revealed no local reactions during this subsequent challenge phase (Ref. 4). A study of infants and children with respiratory infection who received an ointment containing a mixture of volatile oils including eucalyptus oil 1.3 percent applied to the chest and neck demonstrated no adverse effect from inhaled vapors by that route of administration on the rate of clearing of laryngeal edema (Ref. 5). A liquid mixture of volatile substances including eucalyptus oil 1.7 percent is placed in the water of a hot steam vaporizer and administered via inhalation. Exaggerated use studies in adults and children, i.e., exposure for several hours to higher than recommended exposure concentrations either due to sitting in closer proximity to the vaporizer or placing 2 to 5 times the recommended dose of the volatile substance in the vaporizer, was not associated with irritating or toxic effects (Refs. 6 and 7).

A series of studies assessing buccal safety and overt side effects from lozenges containing a mixture of volatile oils was conducted in over 300 subjects. Lozenges containing up to 5.5 mg eucalyptus oil were dissolved in the mouth every hour for 8 hours on 2 successive days. Mild erythema of the buccal mucosa and tongue was observed but did not differ appreciably from the response to dissolving lozenge sugar base without volatile oils. The incidence of gastrointestinal symptoms did not differ from control either (Refs. 8 through 11).

An aerosolized dosage form of volatile substances including 1 percent eucalyptus oil has also been utilized for treatment of nasal congestion. In humans, such aerosol sprays have been generally safe when used as directed but there have been reports of deaths from deliberate sniffing abuse, particularly when the subject inhales from a plastic bag into which the material has been sprayed (Ref. 12). Furthermore, one commercial preparation containing a particular solvent, 1,1,1-trichloroethane, was recently recalled from the market due to potential hazards of this substance (Ref. 13).

(2) *Effectiveness.* There are no well-controlled studies documenting the effectiveness of eucalyptol/eucalyptus oil (topical/inhalant) as a nasal decon-

gestant. Its effectiveness is uncertain due to lack of properly controlled studies of the substance by itself.

In a study of nine patients with head colds, which was not double-blinded or placebo controlled, inhalation of 50 ml volume of eucalyptus vapors did not induce a significantly decreased airway resistance as measured by anterior rhinometry. Increasing the inhaled volume to 300 ml of eucalyptus oil vapors did induce a significant decrease in airway resistance for 15 minutes, but this was followed by increased nasal resistance over the next 100 minutes (Ref. 14). Other studies involving objective measurement of nasal decongestant activity of eucalyptus oil involved mixtures of volatile substances topically applied as ointments (Refs. 15 through 17), in steam inhalations (Refs. 18 and 19) and room aerosol sprays (Refs. 20 through 23). In these studies, although significant nasal decongestant activity as compared to placebo was demonstrated, whether the eucalyptus oil component contributed to this effect is not evident.

The effect of rinsing and gargling twice daily with an aqueous mixture of volatile substances on the incidence of colds and the severity of the symptoms associated with colds was evaluated in a long-term double-blind placebo-controlled subjective study in school children. The results of the study revealed milder nasal symptoms and cough symptoms in individuals using the medicated mouthwash as compared to the placebo. Although the medicated mouthwash contained 0.91 mg/ml eucalyptol, the results did not demonstrate the contribution of this component to the overall alleviation of symptoms (Ref. 24).

(3) *Proposed dosage.* Dosage for adults and children 2 to under 12 years is as follows: (i) For topical use as a 1.3 percent ointment preparation: To be rubbed on the throat, chest, and back as a thick layer. The area of application may be covered. However, clothing should be left loose about the throat and chest to help the vapors rise to reach the nose and mouth. Applications may be repeated up to 3 times daily.

(ii) For steam inhalation use as a 1.7 percent solution: 1 tablespoonful of solution per quart of water is added directly to the water in a hot steam vaporizer, bowl or washbasin; or 2 teaspoonfuls of solution per pint of water are added to an open container of boiling water. Breathe in vapors during the period of medicated steam generation. May be repeated 3 times daily.

(iii) For inhalation use as a 1 percent room spray: Spray room for 15 to 20 seconds in the vicinity of the patient. May be repeated at ½ to 1 hour intervals as needed.

(iv) For topical use as a lozenge 0.2 to 15.0 mg: Allow lozenge to dissolve slowly in mouth. May be repeated every ½ to 1 hour.

(v) For use as a mouthwash 0.91 mg/ml solution: Gargle with ⅔ oz (20 ml) twice daily.

For children under 2 years, there is no recommended dosage except under the advice and supervision of a physician.

(4) *Labeling.* The Panel recommends the Category I labeling for nasal decongestant active ingredients. (See part VIII. paragraph B.1. above—Category I Labeling.) In addition, the Panel recommends the following specific labeling: (i) For topical ointment use: *Warning:* "For external use only. Do not take by mouth or place in nostrils".

(ii) For steam inhalation use: *Warning:* "For steam inhalation only. Do not take by mouth".

(5) *Evaluation.* The Panel made the following recommendations: (i) For topical ointment use: Data to demonstrate effectiveness will be required in accordance with the guidelines set forth below for testing nasal decongestant drugs. (See part VIII. paragraph C. below—Data Required for Evaluation.)

(ii) For steam inhalation use: Data to demonstrate effectiveness will be required in accordance with the guidelines set forth below for testing nasal decongestant drugs. (See part VIII. paragraph C. below—Data Required for Evaluation.)

(iii) For inhalation use as a room spray: Data to demonstrate effectiveness will be required in accordance with the guidelines set forth below for testing nasal decongestant drugs. (See part VIII. paragraph C. below—Data Required for Evaluation.)

(iv) For topical use as a lozenge: Data to demonstrate effectiveness will be required in accordance with the guidelines set forth below for testing nasal decongestant drugs. (See part VIII. paragraph C. below—Data Required for Evaluation.)

(v) For use as a mouthwash: Data to demonstrate effectiveness will be required in accordance with the guidelines set forth below for testing nasal decongestant drugs. (See part VIII. paragraph C. below—Data Required for Evaluation.)

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h. *Menthol/peppermint oil (topical/inhalant).* The Panel concludes that menthol/peppermint oil is safe in the dosage ranges used when applied topically or as an inhalant but there are insufficient data to permit final classification of its effectiveness for topical or inhalant OTC use as a nasal decongestant.

(1) *Safety.* Clinical experience has confirmed that menthol/peppermint oil (topical/inhalant) is safe in the dosage ranges used as a nasal decongestant.

Menthol is the chief constituent of peppermint oil, comprising not less than 50 percent, and may be obtained by distillation of the oil or by synthesis (Ref. 1). Toxic effects with an excess ingestion of peppermint oil or mentholated products can include abdominal pain, nausea, vomiting and symptoms of central nervous system depression such as dizziness, staggering gait, slowed respiration, flushed face, sleepiness and coma (Refs. 2 and 3). The fatal oral dose of menthol itself in man is about 2 gm (Ref. 4). Topically applied menthol produces a cooling sensation presumably due to

stimulation of the cold sensory receptors, whereas higher concentrations have irritant properties. In one study, a 20 percent solution of menthol in oil rubbed on to the skin induced an intense and lasting cooling sensation followed by numbness with slight burning and skin redness. A 0.5 percent solution applied to the nasal or oral mucosa was subjectively irritating whereas a 0.2 percent solution was judged nonirritating (Ref. 5). A study of 223 subjects in which an ointment containing several volatile substances including menthol 2.8 percent was applied for 48 hours to both areas of intact skin under a patch and to abraded skin revealed no instances of inflammation, wheal, hives or primary irritation following the period of exposure (Ref. 6). Repeated topical application of mentholated products has been reported to give rise to hypersensitivity reactions including contact dermatitis (Ref. 4). A study of 10 subjects who received application of an ointment containing several volatile substances including menthol 2.8 percent to their trunks 3 times daily for 3 weeks, then 1 week off followed by another week of treatment, revealed no local reactions during this subsequent challenge phase (Ref. 7). The incidence of hypersensitivity to menthol appears to increase with increased duration of use. For example, one survey revealed an incidence of less than 1 percent menthol hypersensitivity in 542 patients using a mentholated ointment for less than 10 years whereas an incidence of 3.4 percent hypersensitivity was seen in 144 patients using this type of a preparation for longer than 10 years (Ref. 8).

In infants and small children nasal ointment or drops containing menthol may cause spasm of the glottis and cases of dangerous asphyxiation have been reported in infants following local application of menthol. For this reason a warning against the topical application of menthol-containing products directly to the nostrils of infants has been recommended (Refs. 4 and 9). A study of infants and children with respiratory infection who received an ointment containing a mixture of volatile oils including a 2.8 percent menthol applied to the chest and neck demonstrated no adverse effect from the inhaled vapors by that route of administration on the rate of clearing of laryngeal inflammation. In this study 35 children (23 under 2 years of age) with respiratory infection received only standard forms of therapy, e.g., antibiotics and fluids, while 37 children (30 under 2 years of age) received standard therapy plus the mentholated ointment to the chest and neck. Laryngoscopic examination revealed comparable rates of clearing of laryngeal inflammation (Ref. 10).

A liquid mixture of volatile substances including 3.66 percent menthol is placed in the water of a hot steam vaporizer and administered via inhalation. A number of studies involving nearly 900 subjects in which this mixture was administered at recommended doses was not associated with significant complaints of subjectively perceived adverse effects (Refs. 11 through 23). Exaggerated use studies in adults and children, i.e., exposure for several hours to higher than recommended exposure concentrations either due to sitting in closer proximity to the vaporizer or placing 2 to 5 times the recommended dose of the volatile substance in the vaporizer, was not associated with irritating or toxic effects (Refs. 24 and 25).

In two studies involving 40 healthy subjects who were asked to dissolve 2 candy-base lozenges every 20 minutes for 2 hours, each containing 1.36 mg of menthol together with other volatile oils, exhibited no adverse effects with the exception of one report of nausea and vomiting. This was attributed to a dislike for the wild cherry flavor of the lozenge (Refs. 26 and 27). In a group of 70 healthy subjects (50 adults and 20 children, ages 8 to 12), half of the subjects dissolved a menthol-eucalyptus lozenge, 9.62 mg menthol and 5.55 mg eucalyptus oil, every hour for 8 hours on 2 successive days, the other half dissolved the cough drop base without the aromatics. In this intensive dosage schedule, a slightly larger number of subjects demonstrated mild irritation of the oral mucosa on days 1 and 2, but there were no differences between the two groups in the severity of irritation or residual findings after day 2. No systemic complaints were reported (Ref. 28). A similar study using a lozenge formulation containing menthol 8.14 mg and eucalyptus oil 4.625 mg versus a lozenge base without volatile substances produced comparable results (Ref. 29).

An aerosolized dosage form of volatile substances including 1 percent menthol has also been utilized for treatment of nasal congestion and cough symptoms. Rats exposed to acute overdoses of the spray in a confined chamber for 6 hours revealed no untoward behavorial response or airway tissues abnormality upon autopsy examination (Ref. 30). A group of four monkeys were exposed to 200 gm per day of the aerosol, i.e., 2 gm of menthol total dose in divided doses over an 8 hour period for 14 consecutive days in a confined chamber. Eye irritation was the only pharmacotoxic sign observed during the study (Ref. 31). In humans, such aerosol sprays have been generally safe when used as directed but there have been reports of deaths from deliberate sniffing abuse, particularly when the subject inhales from a plastic bag into which the material has been sprayed (Ref. 32). Furthermore, one commercial preparation containing a particular solvent, 1,1,1-trichloroethane, was recently recalled from the market due to potential hazards of this substance (Ref. 33).

(2) *Effectiveness.* There are no well-controlled studies documenting the effectiveness of menthol/peppermint oil (topical/inhalant) as a nasal decongestant. Its effectiveness is uncertain due to lack of properly controlled studies of the substance by itself.

Menthol has been used in external preparations for its effects in the nasal passages. A decided cooling sensation is noticed when the substance is applied to the skin or to the mucous membrane. A cooling sensation noted in nasal passages is associated with a feeling of decreased nasal congestion. The cooling sensation, however, is not associated with an actual decrease in surface temperature, thus it is not dependent upon nasal constriction but rather appears to result from an influence on sensory nerve endings responsible for cold reception (Ref. 34). Standard texts, in fact, have noted that the feeling of nasal decongestion accompanying menthol vapor action may be an illusion and, in fact, may be accompanied by increased congestion (Ref. 1).

Using an electronic technique for measuring nasal airflow in 18 infants and children, Noller demonstrated that intranasal application of a 2.82 percent mentholated ointment induced a reduction in airflow during the first 20 minutes which was followed by an increase in airflow over the pretreatment level, lasting 1 to 3 hours (Ref. 35). In three children the menthol ointment was applied to the chest and back with one nostril remaining closed throughout the experiment except during measurement. Increased airflow was noted only in the open nostril up to 4 hours after administration, leading to the conclusion that the effect of menthol was due to the inhaled vapors (Ref. 35).

In a study of 50 patients with head colds, 15 of whom also received a petrolatum placebo application, application to the chest of an ointment containing a mixture of volatile substances including 2.8 percent menthol induced a significant degree of nasal decongestion compared to placebo over an 8 hour period as determined by a modified Butler-Ivy procedure (Ref. 36). Two additional objective-measurement placebo-controlled crossover studies involving chest, throat and back application of an ointment containing a mixture of volatile substances including 2.8 percent menthol revealed a significant nasal decongestant effect compared to placebo over an 8 hour period in a total of 90 patients with head colds (Refs. 37 and 38).

A liquid mixture of volatile substances which is to be added to the water in a hot steam vaporizer and administered via inhalation contains menthol 3.66 percent, camphor 7 percent, eucalyptus oil 1.7 percent and tincture of benzoin 5 percent. Two objective-measurement placebo-controlled studies in patients with nasal congestion due to head cold revealed that this liquid containing volatile substances placed in hot water in a dose of 1 tablespoon per quart induced a statistically significant decrease in nasal airway resistance compared to inhalation of steam alone during the period of steam inhalation (Refs. 24 and 39). It was demonstrated that an optimal distance between the subject and the vaporizer to elicit this effect was 4 to 6 feet (Ref. 24).

An aerosolized mixture of volatile substances to be sprayed in the room and containing menthol 1 percent and eucalyptus oil 1 percent has been studied for its nasal decongestant effect by ob-

jective measurement studies. When sprayed into the room for 15 seconds in the vicinity of the subject's head, measurement of expiratory nasal flow rate in 25 head cold patients revealed at least a 20 percent increase in expiratory flow rate in 19 of the patients when compared to pretreatment control readings. No placebo was utilized, however, and since measurements were only made for 6 minutes after drug administration, the average duration of effect was not determined (Ref. 40). In a subsequent study on five patients with head colds, the aerosolized mixture of volatile substances readministered at 0, 2, 4 and 7 hours led to a transient increase in expiratory nasal flow rate over the pretreatment level each time. Duration of this effect following each dose was not determined (Ref. 41). In an objective-measurement placebo-controlled study of 15 patients with head colds, nasal airway resistance was determined following a 20-second placebo aerosol spray and then for 30 minutes after a 20-second spraying of the volatile oil mixture which provided a total of 20 gm of aerosolized material. A significant decrease in nasal airway resistance was obtained with the medicated aerosol compared to placebo in 9 of the 15 subjects, but in only 3 of these subjects did the effect persist throughout the 30-minute period of observation (Ref. 42). A similar study with an additional 15 patients having partial nasal congestion due to head colds revealed comparable results (Ref. 43).

Use of a sensitive gas chromatographic technique has revealed the presence of menthol vapors in air expired through the nasal passage during the time a menthol-containing lozenge was dissolving in the subject's mouth (Ref. 44). Patients with nasal congestion due to head colds were divided into 2 groups of 15 each. One group received a 4.27 gm lozenge containing 0.15 percent menthol and 0.04 percent eucalyptus oil while the other group received a nonmedicated lozenge base. No significant difference in nasal airway resistance between the placebo and active medication group could be demonstrated (Ref. 45). In a subjective evaluation study using allergic rhinitis patients, 78.4 percent of the patients using the menthol-eucalyptol lozenge compared to 65.4 percent of the placebo groups claimed relief of their stuffy nose after 1 day of treatment. The difference between the groups was not, however, statistically significant (Ref. 46).

The effect of rinsing and gargling twice daily with an aqueous mixture of volatile substances on the incidence of colds and the severity of the symptoms associated with colds was evaluated in a long-term double-blind placebo-controlled subjective study in school children. The results of the study revealed milder nasal symptoms and cough symptoms in individuals using the medicated mouthwash as compared to the placebo. Although the medicated mouthwash contained 0.42 mg/ml menthol, the results did not demonstrate the contribution of this component to the overall alleviation of symptoms (Ref. 47).

(3) *Proposed dosage.* Dosage for adults and children 2 to under 12 years is as follows: (i) For topical use as a 2.8 percent ointment preparation: To be rubbed on the throat, chest, and back as a thick layer. The area of application may be covered. However, clothing should be left loose about the throat and chest to help the vapors rise to reach the nose and mouth. Applications may be repeated up to 3 times daily.

(ii) For steam inhalation use as a 3.66 percent solution: 1 tablespoonful of solution per quart of water is added directly to the water in a hot steam vaporizer, bowl or washbasin; or 2 teaspoonfuls of solution per pint of water are added to an open container of boiling water. Breathe in vapors during the period of medicated steam generation. May be repeated 3 times daily.

(iii) For inhalation use as a 1 percent room spray: Spray room for 15 to 20 seconds in the vicinity of the patient. May be repeated at ½ to 1 hour intervals as needed.

(iv) For topical use as a lozenge 1.0 to 10 mg: Allow lozenge to dissolve slowly in mouth. May be repeated every ½ to 1 hour.

(v) For use as a mouthwash 0.42 mg/ml solution: Gargle with ⅔ oz (20 ml) twice daily.

For children under 2 years, there is no recommended dosage except under the advice and supervision of a physician.

(4) *Labeling.* The Panel recommends the Category I labeling for nasal decongestant active ingredients. (See part VIII. paragraph B.1. above—Category I Labeling.) In addition, the Panel recommends the following specific labeling: (i) For topical ointment use: *Warning:* "For external use only. Do not take by mouth or place in nostrils".

(ii) For steam inhalation use: *Warning.* "For steam inhalation only. Do not take by mouth".

(5) *Evaluation.* The Panel made the following recommendations: (i) For topical ointment use: Data to demonstrate effectiveness will be required from one additional controlled objective measurement study in patients with nasal congestion due to acute rhinitis in accordance with the guidelines set forth below for testing nasal decongestant drugs. (See part VIII. paragraph C. below—Data Required for Evaluation.)

(ii) For steam inhalation use: Data to demonstrate effectiveness will be required in accordance with the guidelines set forth below for testing nasal decongestant drugs. (See part VIII. paragraph C. below—Data Required for Evaluation.)

(iii) For inhalation use as a room spray: Data to demonstrate effectiveness will be required in accordance with the guidelines set forth below for testing nasal decongestant drugs. (See part VIII. paragraph C. below—Data Required for Evaluation.)

(iv) For topical use as a lozenge: Data to demonstrate effectiveness will be required in accordance with the guidelines set forth below for testing nasal decongestant drugs. (See part VIII. paragraph C. below—Data Required for Evaluation.)

(v) For use as a mouthwash: Data to demonstrate effectiveness will be required in accordance with the guidelines set forth below for testing nasal decongestant drugs. (See part VIII. paragraph C. below—Data Required for Evaluation.)

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(47) OTC Volume 040278.

1. *Phenylpropanolamine hydrochloride (topical).* The Panel concludes that phenylpropanolamine hydrochloride is safe in the dosage ranges used when applied topically but there are insufficient data to permit final classification of its effectiveness for topical OTC use as a nasal decongestant.

(1) *Safety.* Clinical experience has confirmed that phenylpropanolamine hydrochloride (topical) is safe in the dosage ranges used as a nasal decongestant. Phenylpropanolamine hydrochloride as 1 to 5 percent aqueous solution administered by drops or intranasal tampon was well tolerated by most patients, although a few complained of transitory stinging (Refs. 1, 2, and 3). Rhinoscopic examination revealed little or no evidence of nasal irritation following prolonged and continuous use of 3 percent phenylpropanolamine nasal solution but details of time parameters of drug administration were not given (Ref. 2). There is a need for additional data relating frequency of use with incidence and intensity of rebound nasal congestion in adults and children.

(2) *Effectiveness.* There are no well-controlled studies documenting the effectiveness of phenylpropanolamine hydrochloride (topical) as a nasal decongestant. Its effectiveness is uncertain because no properly controlled objective measurement studies have been presented.

Phenylpropanolamine hydrochloride is generally considered to exert a nasal decongestant effect when topically applied as a 1 to 3 percent solution (Refs. 1 through 5). Administration as drops or soaked intranasal tampons (3 to 5 minutes contact time) to adult chronic rhinitis patients resulted in subjective and rhinoscopic evidence of nasal decongestion persisting up to 2 hours. None of these studies were controlled, double-blind or contained objective measurements in their design. No data from studies in children were presented. Studies of nasal decongestant effectiveness of topical phenylpropanolamine hydrochloride in 0.25 percent to 0.5 percent concentrations are currently in progress and the Panel was told that a report will be submitted when completed (Ref. 6).

(3) *Proposed dosage.* Adults and children above 6 to under 12 years topical dosage is 2 to 3 drops or sprays of a 1 percent solution in each nostril every 2 to 4 hours. For children under 6 years, there is no recommended dosage except under the advice and supervision of a physician. Concentrations and frequency of administration for safe and effective use have not been established in children under 6 years.

(4) *Labeling.* The Panel recommends the Category I labeling for nasal decongestant active ingredients. (See part VIII. paragraph B.1. above—Category I Labeling.)

(5) *Evaluation.* Data to demonstrate effectiveness will be required in accordance with the guidelines set forth below for nasal decongestant drugs. (See part VIII. paragraph C. below—Data Required for Evaluation.)

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j. *Thenyldiamine hydrochloride (topical).* The Panel concludes that thenyldiamine hydrochloride is safe in the dosage ranges used when applied topically but there are insufficient data to permit final classification of thenyldiamine hydrochloride as safe and effective for OTC use as a topical nasal decongestant.

(1) *Safety.* Clinical experience has confirmed that thenyldiamine hydrochloride (topical) is safe in the dosage ranges used as a nasal decongestant. Topically, 0.1 percent or 0.2 percent thenyldiamine hydrochloride in combination with phenylephrine hydrochloride, 0.25 and 0.5 percent, produced only "slight" or "moderate" stinging in some of the subjects in human intranasal irritation studies conducted by a manufacturer (Ref. 1). Preparations containing 0.5 percent thenyldiamine hydrochloride produced "moderate" to "severe" stinging in all subjects and irritation of the larynx in a few subjects. There are no data available on the incidence of rebound congestion.

(2) *Effectiveness.* There are no well-controlled studies documenting the effectiveness of thenyldiamine hydrochloride (topical) as a nasal decongestant. In a randomized, double-blind, and

crossover study of patients with acute rhinitis, a combination of thenyldiamine hydrochloride, 0.1 percent, with other active ingredients applied intranasally as a sprayed solution produced a subjectively evaluated nasal decongestant effect which was significant as compared to that produced by a placebo solution (Ref. 2). However, in this study the effectiveness of the combination product, thenyldiamine with phenylephrine and benzalkonium, was not significantly different from that of the product minus thenyldiamine. In fact, the nasal decongestant effect produced by phenylephrine alone and the nasal decongestant effect produced by thenyldiamine alone were not significantly different from the nasal decongestant effect produced by the combination commercial product. The three preparations did not differ at the 95 percent confidence level.

In another controlled study to determine the therapeutic contribution of topically applied thenyldiamine in a combination product with phenylephrine and benzalkonium chloride, no additive or synergistic effect was evident over that obtained by phenylephrine 0.5 percent alone, when measured by posterior electronic rhinometry or by a plethysmograph with a face mask (Ref. 3).

The manufacturer's labeling states that thenyldiamine hydrochloride "offsets the results of mediator release to the extent it is producing obstruction and at the same time opposes cholinergic hyperemia and rhinorrhea." Thacker (Ref. 4) supports inclusion of antihistamines in OTC nasal decongestant products to prevent engorgement from migration of excessive body fluids from the vascular system into tissue spaces and to aid in alleviating allergic reactions to ingredients in the solution. This supposition, however, is not supported by scientific evidence.

Studies with topical thenyldiamine indicate it may be a nasal decongestant but no nasal decongestant claims are made for this ingredient in the commercially available OTC products, although the products themselves are nasal decongestants. Present claims made for thenyldiamine are based on topical application of an antihistamine but there are no studies on the antihistamine activity of the drug applied topically.

There are no data on the use of this drug in children.

(3) *Proposed dosage.* Adult topical dosage is 1 to 3 drops or sprays of a 0.1 percent solution in each nostril not more than every 4 hours. For children under 12 years, there is no recommended dosage except under the advice and supervision of a physician.

(4) *Labeling.* The Panel recommends the Category I labeling for nasal decongestant active ingredients. (See part VIII. paragraph B.1. above—Category I Labeling.)

(5) *Evaluation.* Data to demonstrate effectiveness will be required in accordance with the guidelines set forth below for nasal decongestant drugs. (See part VIII. paragraph C. below—Data Required for Evaluation.)

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(3) Gould, W. J., "Clinical Summary of NTZ Study, MRD, 70–65," Draft of unpublished paper is included in OTC Volume 040298.

(4) Thacker, E. A., "Nasal Solutions with Combined Therapeutic Effects," *The Eye, Ear, Nose and Throat Monthly*, 29:609–613, 1950.

k. *Thymol (topical/inhalant).* The Panel concludes that thymol is safe in the dosage ranges used when applied topically or as an inhalant but there are insufficient data to permit final classification of its effectiveness for topical/inhalant OTC use as a nasal decongestant.

(1) *Safety.* Clinical experience has apparently confirmed that thymol (inhalant) is safe in the dosage ranges used as a nasal decongestant.

Thymol is an alkyl derivative of phenol and has bactericidal, fungicidal, and anthelmintic properties (Ref. 1). When hydrogenated, thymol is converted to the closely related drug, menthol (Ref. 2). The LD_{50} of thymol in mice is 1,800 mg/kg orally (Ref. 3). No data were found bearing on the drug's toxicity in man. In view of thymol's relative inactivity compared to menthol, of which 50 to 120 gm "would have to be absorbed to cause poisoning" (Ref. 4), thymol is presumed to be relatively nontoxic.

(2) *Effectiveness.* There are no well-controlled studies documenting the effectiveness of thymol (inhalant) as a nasal decongestant. Experiments in anesthetized rabbits have indicated that thymol administered by steam inhalation augmented the concentration of soluble mucous in the respiratory tract fluid (Ref. 2). The dose administered was unknown but the concentration in the vaporizer was in excess of 81 mg/kg. The volume of secretions did not change. Much lower concentrations of menthol were effective (1 mg/kg). In man no data on effectiveness of thymol alone were found although a mixture containing thymol, menthol, eucalyptol, and propylene glycol appeared to suppress citric acid induced cough (Ref. 5) and to reduce resistance in the nasal and bronchial airways (Ref. 6).

Studies involving the objective measurement of the nasal decongestant activity of thymol were done with mixtures of volatile substances, topically applied as ointments (Refs. 7, 8 and 9), and in steam inhalations (Refs. 10 and 11). Although significant nasal decongestant activity as compared to placebo was demonstrated, it was not evident whether the thymol component contributed to this effect.

The effect of rinsing and gargling twice daily with an aqueous mixture of volatile substances on the incidence of colds and the severity of the symptoms associated with colds was evaluated in a long-term double-blind placebo-controlled subjective study in school children. The results of the study revealed milder nasal symptoms in individuals using the medicated mouthwash as compared to the placebo. Although the medicated mouthwash contained 0.63 mg/ml thymol, the results did not demonstrate the contribution of this component to the overall alleviation of symptoms (Ref. 12).

(3) *Proposed dosage.* Dosage for adults and children 2 to under 12 years is as follows: (i) For topical use as a 0.1 percent ointment preparation: To be rubbed on the throat, chest, and back as a thick layer. The area of application may be covered. However, clothing should be left loose about the throat and chest to help the vapors rise to reach the nose and mouth. Applications may be repeated up to 3 times daily.

(ii) For steam inhalation use as a 0.13 percent solution: 1 tablespoonful of solution per quart of water is added directly to the water in a hot steam vaporizer, bowl or washbasin; or 2 teaspoonfuls of solution per pint of water are added to an open container of boiling water. Breathe in vapors during the period of medicated steam generation. May be repeated 3 times daily.

(iii) For inhalation use as a 0.1 percent room spray: Spray room for 15 to 20 seconds in the vicinity of the patient. May be repeated at ½ to 1 hour intervals as needed.

(iv) For topical use as a lozenge 0.02 to 2.0 mg: Allow lozenge to dissolve slowly in mouth. May be repeated every ½ to 1 hour.

(v) For use as a mouthwash 0.63 mg/ml solution: Gargle with ⅔ oz (20 ml) twice daily.

For children under 2 years, there is no recommended dosage except under the advice and supervision of a physician.

(4) *Labeling.* The Panel recommends the Category I labeling for nasal decongestant active ingredients. (See part VIII. paragraph B.1. above—Category I Labeling.) In addition, the Panel recommends the following specific labeling: (i) For topical ointment use: *Warning:* "For external use only. Do not take by mouth or place in nostrils".

(ii) For steam inhalation use: *Warning:* "For steam inhalation only. Do not take by mouth".

(5) *Evaluation.* The Panel made the following recommendations: (i) For topical ointment use: Data to demonstrate effectiveness will be required in accordance with the guidelines set forth below for testing nasal decongestant drugs. (See part VIII. paragraph C. below—Data Required for Evaluation.)

(ii) For steam inhalation use: Data to demonstrate effectiveness will be required in accordance with the guidelines set forth below for testing nasal decongestant drugs. (See part VIII. paragraph C. below—Data Required for Evaluation.)

(iii) For inhalation use as a room spray: Data to demonstrate effectiveness will be required in accordance with the guidelines set forth below for testing nasal decongestant drugs. (See part VIII. paragraph C. below—Data Required for Evaluation.)

(iv) For topical use as a lozenge: Data to demonstrate effectiveness will be required in accordance with the guidelines set forth below for testing nasal decongestant drugs. (See part VIII. paragraph C. below—Data Required for Evaluation.)

(v) For use as a mouthwash: Data to demonstrate effectiveness will be required in accordance with the guidelines set forth below for testing nasal decongestant drugs. (See part VIII. paragraph C. below—Data Required for Evaluation.)

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(10) Shapiro, M., "Steam Alone vs. Vaposteam in Steam," Draft of unpublished data is included in OTC Volume 040298.

(11) Ciampi, L. A., "Vaposteam. Nasal Decongestant Vick Rhinorrheometer. CRD 75–1," Draft of unpublished data is included in OTC Volume 040298.

(12) OTC Volume 040278.

1. *Turpentine oil (spirits of turpentine) (topical/inhalant).* The Panel concludes that turpentine oil is safe in the dosage ranges used when applied topically or as an inhalant but there are insufficient data to permit final classification of its effectiveness for topical or inhalant OTC use as a nasal decongestant.

(1) *Safety.* Clinical experience has confirmed that turpentine oil (topical/inhalant) is safe in the dosage ranges used as a nasal decongestant.

Oil of turpentine is a volatile oil consisting of a mixture of pinenes derived from the oleoresin obtained from *Pinus palustris*. Nelson et al. (Ref. 1) found exposure to a vapor of 420 to 560 mcg/l acceptable to most of their human subjects. The threshold for industrial exposure for 8 hours has been set at 560 mcg/l. The maximum concentration obtainable with a currently marketed OTC preparation is 36 mcg/l (Refs. 2 and 3). No histological evidence of pulmonary lesions were seen in mice and rats exposed to lethal concentrations of turpentine vapors (Ref. 4). Inhalation of 300 mcg/l of turpentine vapor by mice for 15 minutes did not influence the electrocardiogram, respiratory minute volume, pulmonary airway resistance or compliance (Ref. 5). One study conducted in mice using a mixture of volatile oils, one of which was turpentine, showed a decrease in pulmonary antibacterial activity (Ref. 6). Two other studies showed no change when the mixture was used (Refs. 7 and 8).

In several studies in children and infants suffering from minor breathing discomforts associated with the "common cold" no side effects that were drug related were observed when a medicated steam was administered (Refs. 9 through 13). Turpentine has been widely used as a part of a mixture of volatile oils for many years with approximately two complaints per million packages purchased (Ref. 14).

(2) *Effectiveness.* Studies involving the objective measurement of the nasal decongestant activity of turpentine were done with mixtures of volatile substances, topically applied as ointments (Refs. 15, 16, and 17), and in steam inhalation (Refs. 18 and 19). Although significant nasal decongestant activity as compared to placebo was demonstrated in these studies, it was not evident whether the turpentine contributed to this effect.

(3) *Proposed dosage.* Dosage for adults and children 2 to under 12 years is as follows: (i) For topical use as a 4.0 percent ointment preparation: To be rubbed on the throat, chest, and back as a thick layer. The area of application may be covered. However, clothing should be left loose about the throat and chest to help the vapor rise to reach the nose and mouth. Applications may be repeated up to 3 times daily.

(ii) For steam inhalation use as a 5.5 percent solution: 1 tablespoonful of solution per quart of water is added directly to the water in a hot steam vaporizer, bowl, or 2 teaspoonfuls of solution per pint of water are added to an open container of boiling water. Breathe in vapors during the period of medicated steam generation. May be repeated 3 times daily.

For children under 2 years, there is no recommended topical or inhalant dosage except under the advice and supervision of a physician.

(4) *Labeling.* The Panel recommends the Category I labeling for nasal decongestant active ingredients. (See part VIII. paragraph B.1. above—Category I Labeling.) In addition, the Panel recommends the following specific labeling: (i) For topical ointment use: *Warning:* "For external use only. Do not take by mouth or place in nostrils".

(ii) For steam inhalation use: *Warning:* "For steam inhalation only. Do not take by mouth".

(5) *Evaluation.* The Panel made the following recommendations: (i) For topical ointment use: Data to demonstrate effectiveness will be required in accordance with the guidelines set forth below for testing nasal decongestant drugs. (See part VIII. paragraph C. below—Data Required for Evaluation.)

(ii) For steam inhalation use: Data to demonstrate effectiveness will be required in accordance with the guidelines set forth below for testing nasal decongestant drugs. (See part VIII. paragraph C. below—Data Required for Evaluation.)

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(17) Carter, V. H., "Vaporub. Nasal Decongestant Study—Vick Rhinorrheometer. CRD 72–7," Draft of unpublished data is included in OTC Volume 040298.

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Category III Labeling

The Panel concludes that the available data are insufficient to permit final

classification of the labeling claims identified below for nasal decongestants. Additional data are required to support the following nasal decongestant claims:

Reference to "preventing sneezing", "drying runny nose" or "checking post nasal drip" are unsubstantiated claims for nasal decongestants unless studies specifically designed to assess these activities are presented. Studies of nasal decongestants have assessed the effect on nasal airway resistance or the ease of breathing but not the effect on rhinorrhea.

Reference to an indirect effect in "preventing or alleviating cough" by an effect on nasal congestion is an unsubstantiated claim unless studies specifically designed to assess this activity are presented.

Reference to an effect "to reduce sinus pressure" is an unsubstantiated claim since studies of nasal decongestant activity assess the effect on nasal airway resistance. Although it is assumed that this effect on the nasal mucosa may indirectly facilitate sinus drainage and thus decrease sinus congestion, it would be unsubstantiated to claim a drug effect to decrease sinus pressure without evidence to support this claim.

Reference to the extent of the penetration of topically applied nasal decongestants is unsubstantiated without specific studies to demonstrate the extent of penetration (depth of penetration into the nasal cavity and/or the extent of penetration into the nasal mucosa).

Pressure within the antrum can be measured and recorded in terms of centimeter of water compared to ambient pressure by means of a suitable needle or small trocar placed in the antrum under topical anesthesia. This would be performed in a small number of patients (5 to 10) with nasal congestion associated with an acute respiratory infection who complain of localized headache and/or tenderness in the sinus areas. These pressure measurements would be repeated following the administration of the test preparation or placebo in the dosage range and time intervals recommended for OTC usage. Subjective symptoms such as headache, tenderness, etc., could be evaluated in conjunction with the pressure measurements.

C. DATA REQUIRED FOR EVALUATION

The Panel has agreed that the protocols recommended in this document for the studies required to bring a Category III drug into Category I are in keeping with the present state of the art and do not preclude the use of any advances or improved methodology in the future.

1. *Principles in the design of an experimental protocol for testing nasal decongestant drugs.* a. *General principles.* The effectiveness of a nasal decongestant drug should be determined by its ability to reduce nasal obstruction in patients with acute or chronic rhinitis. Tests should involve double-blind placebo-controlled assessment of the drug's ability to decrease nasal airway resistance. Patient-reported subjective assessment is also desirable. The drugs used should be the same as in the OTC preparation and should be given in the same dosage as the recommended label instructions for the preparation. Since either oral or topical nasal decongestants may be administered repeatedly during episodes of nasal congestion, studies should bear on the appropriate interval for dosing to maintain optimal relief of symptoms. For locally applied nasal decongestants, wherein rebound congestion with repeated use is a concern, labeling should specify short-term use in providing temporary relief of nasal congestion. Specific data on this matter should be obtained by testing the topical nasal decongestant in the concentrations and maximal dosage frequencies to be recommended for periods of at least 1 week in order to assess the incidence and severity of a drug-induced increase in nasal airway resistance.

b. *Selection of patients.* Selection of patients for testing should be based on the diagnosis of rhinitis with nasal congestion. Patients with chronic allergic or vasomotor rhinitis present relatively stable nasal congestion and consequently can serve as their own controls in a crossover study design. Patients with acute allergic or infectious rhinitis also represent a large proportion of the patient type likely to self-medicate with a nasal decongestant. Because of the relatively brief time course of these acute disorders and greater variation in stability of congestion, larger numbers of these patients would have to be studied by assigning them in random fashion to placebo or drug groups. Further, for comparative purposes these groups have to be matched by age, sex, and if possible, the degree of nasal congestion at the time of study. Smoking by test subjects should be prohibited 24 hours prior to and during the test.

c. *Methods of study.* Observation should include both the subjective response and objectively measured nasal airway resistance before the drug or placebo is administered, and at appropriate intervals thereafter to demonstrate time of onset, magnitude, and duration of response.

d. *Interpretation of data.* A recommended dose of the test drug should induce a statistically significant reduction in nasal airway resistance when compared with the placebo response.

Evidence of drug effectiveness is required from a minimum of two positive studies based on the results of two different investigators or laboratories.

All data submitted to the Food and Drug Administration must present both favorable and any unfavorable results.

e. *Evaluation of safety.* Tests of safety should involve the usual tests for toxicity relevant to the known possible adverse effects of the drugs under testing. Tests should be done in the form of dose response curves up to a maximum therapeutic effectiveness.

IX. MISCELLANEOUS INGREDIENTS

A. GENERAL COMMENT

The action of several drugs considered by the Panel do not fall within the main pharmacologic groups, i.e., antitussives, expectorants, bronchodilators, anticholinergics, antihistamines, and nasal decongestants reviewed by the Panel. However, these miscellaneous ingredients are found in many OTC CCABA products. Because of the differences in their intended action in CCABA products, they are discussed individually below.

B. CATEGORIZATION OF DATA

The miscellaneous ingredients and/or labeling have been reviewed and classified as follows:

1. *Conditions under which CCABA products are not generally recognized as safe and effective or are misbranded.* The use of certain conditions are unsupported by scientific data, and in some instances by sound theoretical reasoning. The Panel concludes that the following ingredients and/or labeling should be removed from the market until scientific testing supports their use.

a. *Antihistamines in combination CCABA products exclusively for sedation.* The Panel concludes that the combining of an antihistamine in a CCABA combination product for the exclusive purpose of sedation is irrational. The Panel is aware that CCABA combination products are currently available for use at bedtime and promoted for such various claims as "for restful sleep". However, the duration of drug effects in "nighttime cold preparations" which are recommended to be taken once at bedtime is not fully documented. Although antihistamines produce sedation as a side effect depending upon the dosage, the addition of an antihistamine for the primary purpose of sedation is not rational. The Panel has recommended the use of antihistamines in CCABA combination products only for the relief of symptoms of allergic rhinitis. (See part II. paragraph C.5.b. above—Combination products containing antihistamines with sleep-aid claims.)

Certain antihistamines are generally considered safe for OTC use. The Panel has recommended specific doses for each of these antihistamines after a consideration of the scientific data available for these ingredients. The Panel concluded that the antihistamines reviewed by the Panel and classified as Category I are both safe and effective for the treatment of the symptoms of allergic rhinitis when administered as labeled. (See part VII. paragraph B.1. above—Category I conditions under which antihistamine ingredients are generally recognized as safe and effective and are not misbranded.) However, the Panel does not recommend the addition of another antihistamine to a CCABA combination product for the exclusive purpose of sedation. The rationale for the use of an additional antihistamine in CCABA combination products for the exclusive purpose of sedation has not been demonstrated.

b. *Vitamins used alone or in combination CCABA products with labeling claims for the prevention or treatment of the "common cold".* The Panel is unaware of any well-controlled studies documenting the safety or effectiveness

of vitamins for use in the prevention or treatment of the "common cold". In addition, the Panel concludes that the use of any vitamin in CCABA combination products for the prevention of colds is irrational since such products should only be used when the symptoms of the "common cold" are present. It would, therefore, be irrational for a consumer to take a cold combination product containing vitamins to prevent a cold. The Panel has discussed this issue earlier in this document. (See part II. paragraph C.5.a. above—Combination products containing vitamins.)

The Panel is aware of the popular use of vitamin C for treatment of the symptoms of the "common cold." However, the Panel has reviewed the available data which is discussed below and concludes that no drug labeling claims should be made for vitamin C for the prevention or treatment of the symptoms of the "common cold" until adequate data are available to substantiate such claims. (See part IX. paragraph B.2.b. below—Ascorbic acid (vitamin C).)

2. *Conditions for which the available data are insufficient to permit final classification at this time.* The Panel concludes that adequate and reliable scientific evidence is not available at this time to permit final classification of the claimed active ingredients for the conditions listed below. The Panel believes it reasonable to provide 3 years for vitamin C, 2 years for phenobarbital and caffeine, and 3 years for antihistamines for the development and review of evidence to substantiate the conditions specified below. Marketing need not cease during this time if adequate testing is undertaken. If adequate effectiveness data are not obtained within the time period provided, the ingredients listed in this category should no longer be marketed as over-the-counter products. The ingredients considered in this category are:

Antihistamines in combination CCABA products with sleep-aid claims

Ascorbic acid (vitamin C)
Caffeine
Phenobarbital

a. *Antihistamines in combination CCABA products with sleep-aid claims.* The Panel concludes that there are insufficient data to permit final classification of the safety and effectiveness for OTC use of sleep-aid claims for antihistamines in combination CCABA products in which their primary claim is for the relief of the symptoms of allergic disorders. The Panel is aware that antihistamines may have several activities, e.g., antitussive, antihistamine or sedative activity, depending on the dosage level used. The Panel has discussed this issue earlier in this document. (See part II. paragraph C.5.b. above—Combination products containing antihistamines with sleep-aid claims.)

(1) *Safety.* Clinical experience has confirmed that antihistamines are safe in the dosage ranges used in combination CCABA products with sleep-aid claims.

The Panel concludes that the antihistamines reviewed by the Panel and classified as Category I are both safe and effective for the treatment of the symptoms of allergic rhinitis when administered as labeled. (See part VII. paragraph B.1. above—Category I conditions under which antihistamine ingredients are generally recognized as safe and effective and are not misbranded.) However, the Panel was unable to make a final definition as to the safe and effective use of antihistamines as sleep-aids in CCABA products.

(2) *Effectiveness.* There are no well-controlled studies documenting the effectiveness of antihistamines in combination CCABA products as sleep-aids. Although sedation may be a side effect, the effectiveness of antihistamines in CCABA combination products as sleep-aids, is not fully understood.

(3) *Proposed dosage.* The Panel is unable to determine a proposed dosage. The Panel concludes that the pharmaceutical industry should consult with the Food and Drug Administration as to a suitable proposed dosage for testing. Otherwise, the Panel recommends that each drug manufacturer evaluate the dosage as labeled on the manufacturer's marketed product(s).

(4) *Labeling.* The Panel recommends that labeling claims contained in each drug manufacturer's currently marketed product, i.e., "for restful sleep", should be used.

(5) *Evaluation.* Data to demonstrate effectiveness will be required to be completed in 3 years. The Panel recommends a testing protocol in conformance with the requirements specified by the OTC Sedative, Tranquilizer and Sleep-Aid Drug Products Panel as published in the FEDERAL REGISTER of December 8, 1975 (40 FR 57292).

b. *Ascorbic acid (vitamin C).* The Panel concludes that there are insufficient data to permit final classification of ascorbic acid as safe and effective for OTC use in the prevention or treatment of the "common cold." The use of vitamin C in CCABA combination products has been discussed earlier in this document. (See part II. paragraph C.5.a. above—Combination products containing vitamins.)

(1) *Safety.* Long experience and innumerable studies attest to the fact that ascorbic acid, in doses preventing scurvy, is entirely safe. The daily requirement of ascorbic acid for the adult man is 30 mg and the National Academy of Sciences-National Research Council has therefore set the daily dietary allowance for ascorbic acid at 45 mg (Ref. 1). Ascorbic acid is probably safe in the dosage used for the treatment of acute catarrhal conditions of the nasal mucous membranes which is usually accompanied with profuse discharge from the nostrils, referred to as coryza. Dosages recommended for prevention or treatment of coryza range from 1 to 3 gm or more daily raising blood levels above the renal threshold with consequent rapid excretion by the kidney. Change from a high to a low level of ascorbic acid in the diet appears to predispose to the development of scurvy (Ref. 2).

In humans, massive doses of vitamin C, from 1 to 10 or more gm per day, have not caused toxic symptoms. Diarrhea is the only symptom reported. High levels of urinary ascorbic acid may give false positive tests for sugar in diabetic patients (Ref. 3). Also, theoretically, large doses of ascorbic acid increase the level of uric and oxalic acid in the urine, a possible hazard in patients with a tendency to gout or oxalate renal stones (Ref. 2). Large doses of vitamin C in laboratory animals have been reported to reduce fertility (Ref. 3). In a large study in human subjects (Ref. 4) the administration of large daily doses of vitamin C caused a marked but transitory fall in the vitamin C content of the blood when the vitamin C was discontinued.

(2) *Effectiveness.* There are no well-controlled studies documenting the effectiveness of vitamin C in the prevention or treatment of the "common cold."

Ten or more studies have left the matter of effectiveness in doubt. None of the studies done to date have shown ascorbic acid in any of the dosage schedules used to be unequivocally effective, although trends in favor of effectiveness have been seen. The need for elimination of bias by careful design of clinical trials has been repeatedly stressed.

The claimed effects of large doses of vitamin C on the "common cold" include prevention of colds, more rapid recovery and reduced severity.

In reviews of the data, Pauling argued persuasively (Refs. 5 through 8) that the data favored a beneficial effect of large dosages of vitamin C in treating the "common cold." In another review of these data more caution is urged in accepting this interpretation (Ref. 3). In a third review (Ref. 9), data presented by the reviewer as well as data from many other studies are interpreted as favoring a beneficial effect of large dosages of vitamin C in treating the "common cold." However, an addendum citing data published in 1974 (Ref. 10) failed to support a beneficial effect in doses ranging from 50 to 1,000 mg of vitamin C daily.

In a double-blind study comprising 1,000 subjects (Ref. 11) receiving a placebo or vitamin C in a dose of 1,000 mg daily and 4,000 mg for each of the first 3 days of a cold, there were 30 percent fewer days of confinement to the house among those receiving vitamin C as compared with those receiving the placebo, a finding that was highly significant ($p=0.001$). A second study indicated that the effect observed was not ascribable to either a prophylactic or a therapeutic effect alone (Ref. 4). A dosage level of 2,000 mg/day was not significantly different in its effects from one of 250 mg/day.

In the third of a series of large-scale double-blind studies on the effect of vitamin C on the "common cold" also recently published, the data indicated that subjects receiving vitamin C either in regular or sustained release forms in a dose of 500 mg each week, 1,500 mg on the first day of a cold and 1,000 mg daily for the next 4 days, had a significantly

milder illness than those receiving a placebo (Ref. 12). These findings indicate that very large daily doses of vitamin C may be unnecessary.

In a recent study (Ref. 13), a random sample of employees in the National Institutes of Health comprising 190 subjects were given prophylactic daily ascorbic acid (3,000 mg) or a placebo and with the onset of a "cold" were given 3,000 mg or 6,000 mg ascorbic acid or a placebo. The study was well-designed with the exception that the placebo differed in taste from the active drug thus leading the investigators to question whether the observed result of "minor influence on the duration and severity of colds" was attributable to this flaw in the study design rather than to a beneficial effect of ascorbic acid.

One means by which vitamin C might favorably influence the "common cold" is suggested by recent in vitro studies showing that in the presence of 250 mcg/ml vitamin C and glutathione, the growth of one of the causes of the "common cold," rhinovirus, was markedly suppressed. This concentration of vitamin C was without an adverse effect on the cells (Ref. 14). In contrast to the implication that vitamin C has a specific antiviral effect, one of the recent clinical studies indicates that vitamin C has a beneficial effect on various types of illnesses and not only the syndrome referred to as the "common cold" (Ref. 11).

The Panel concludes that the published data support a beneficial effect of vitamin C on the severity and perhaps frequency of the "common cold" when given in dosages exceeding the daily requirement. However, it is not yet clear that this effect is clinically significant. The magnitude of the dosages needed and the optimum schedule for prophylaxis and therapy remain to be determined.

(3) *Proposed dosage.* The Panel is unable to determine a proposed dosage. The Panel concludes that the pharmaceutical industry should consult with the Food and Drug Administration as to a suitable proposed dosage for testing.

(4) *Labeling.* The Panel is unable to determine suitable labeling. The Panel concludes that no drug labeling claims should be made for vitamin C for the prevention or treatment of the symptoms of the "common cold" until adequate data are available to substantiate such claims. The Panel has discussed such labeling claims above. (See part IX. paragraph B.1.b. above—Vitamins used alone or in combination CCABA products with labeling claims for the prevention or treatment of the "common cold.") The Panel recognizes that vitamin C is readily available as a food supplement to any consumer who so selects to treat the symptoms of the "common cold."

(5) *Evaluation.* Data to demonstrate effectiveness will be required to be completed in 3 years.

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c. *Caffeine.* The Panel concludes that there are insufficient data to permit final classification of caffeine as safe and effective as a "stimulant corrective" for OTC use in combination CCABA products containing central nervous system sedating drugs, such as the antihistamines. The Panel presumes that caffeine has been added as a "stimulant corrective" rather than as an active ingredient. The Panel has discussed this issue earlier in this document. (See part II. paragraph C.5.e. above—Combination products containing correctives (stimulants and sedatives).)

(1) *Safety.* Clinical experience has confirmed that caffeine is generally considered safe in the doses (15 to 30 mg) commonly contained in CCABA combination products.

The Panel is aware of the OTC Sedative, Tranquilizer and Sleep-Aid Drug Product Panel's findings regarding caffeine which were published in the FEDERAL REGISTER of December 8, 1975 (40 FR 57292). That Panel concluded that caffeine when used alone and not in a combination drug product is safe and effective for use as a stimulant at a recommended dose of 100 to 200 mg not more often than every 3 to 4 hours.

(2) *Effectiveness.* There are no well-controlled studies demonstrating the effectiveness of caffeine as a "stimulant corrective" in combination CCABA products. The Panel is unaware of any data that support such use in combination products.

(3) *Proposed dosage.* The Panel is unable to determine a proposed dosage. The Panel concludes that the pharmaceutical industry should consult with the Food and Drug Administration as to a suitable proposed dosage for testing. Otherwise, the Panel recommends that each drug manufacturer evaluate the dosage as labeled on the manufacturer's marketed product(s).

(4) *Labeling.* The Panel recommends the labeling claims contained in each drug manufacturer's currently marketed products. In addition, the Panel recommends the activity of caffeine should be identified on the label as "an ingredient added to counteract drowsiness caused by other drugs in this product."

(5) *Evaluation.* Data to demonstrate effectiveness as a stimulant corrective will be required to be completed in 2 years. An acceptable test procedure will be one in which the combination with and without the corrective is evaluated to assess the effectiveness of the corrective to significantly decrease the incidence and/or intensity of the undesirable side effect and the safety of this combination.

d. *Phenobarbital.* The Panel concludes that there are insufficient data to permit final classification of phenobarbital as safe and effective for OTC use as a "stimulant corrective" in combination products with central nervous system stimulant drugs, such as the theophyllines and ephedrine. The Panel presumes that phenobarbital has been added as a "sedative corrective" rather than as a CCABA active ingredient. The Panel has discussed this issue earlier in this document. (See part II. paragraph C.5.e. above—Combination products containing correctives (stimulants and sedatives).)

(1) *Safety.* Clinical experience has confirmed that phenobarbital is generally considered safe in the doses recommended for sedative effect.

The generally recognized dose of phenobarbital as a sedative is 15 to 30 mg given 2 to 4 times daily (Refs. 1 through 3). An official compedium gives a range of 50 to 200 mg daily (Ref. 4). Adverse reactions are infrequent. Effective sedation is usually accompanied by lengthened reaction time (Ref. 5). There are occasional reports of megaloblastic anemia on prolonged use (Ref. 3). Phenobarbital stimulates the synthesis of drug-metabolizing enzymes in the liver, which may increase the metabolism (biotransformation) of other drugs administered at the same time. This type of interaction interferes with obtaining a predictable intensity and/or duration of action of other drugs administered during the period of phenobarbital administration (Refs. 1 through 3). Barbiturates, as a class, are subject to abuse. In patients with acute intermittent porphyria, phenobarbital may precipitate a dangerous rise in the level of porphyrins.

(2) *Effectiveness.* Phenobarbital is used in combination products containing

theophyllines and ephedrine, at a dose of 8 mg, to counteract the central nervous stimulant effect of these drugs. However, the effectiveness of phenobarbital as a "sedative corrective" at a dose of 8 mg has not been established.

The generally recognized dose of phenobarbital as a sedative is 15 to 30 mg given 2 to 4 times daily (Refs. 1 through 3). It would be reasonable to expect that if there is stimulation from other drugs such as ephedrine, the dose to antagonize the stimulation should be at least the minimum effective sedation dose. All the citations in the various volumes submitted state only that a barbiturate is useful in counteracting the stimulant effects of drugs like ephedrine. None suggest a dose. Phenobarbital stimulates hepatic enzymes which may increase the metabolism of other drugs and thereby reduce their expected activity (Refs. 1 and 2). It would seem that the only way to determine the effectiveness of an 8 mg dose of phenobarbital and whether it contributes to the combination of antiasthmatic preparations is by conducting controlled clinical trials.

(3) *Proposed dosage.* Adult oral dosage is 8 to 16 mg every 4 hours.

(4) *Labeling.* The Panel recommends the following: (i) *Indications.* The activity of phenobarbital should be identified on the label as "an ingredient added to counteract nervousness caused by other drugs in this product".

(ii) *Warnings.* (*a*) *"Caution:* May cause drowsiness. Avoid driving a motor vehicle or operating heavy machinery".

(*b*) "Do not take this product if you are presently taking other drugs except under the advice and supervision of a rective":

(*c*) "May be habit-forming".

(5) *Evaluation.* Effectiveness at 8 mg has not been established. Further studies must be completed in 2 years. The Panel recommends the following guidelines to establish effectiveness as a "sedative corrective".

a. *General principles.* Sympathomimetic drugs and theophyllines may cause central nervous system stimulation in some patients. To counteract this a small dose of sedative has been added to some combinations. An experimental protocol should be designed to evaluate the effectiveness of the sedative under the above circumstances and, in addition, it is necessary to show whether the sedative has any additional beneficial or adverse effects on bronchospasm.

b. *Selection of patients.* Testing should be based on the diagnosis of asthma. There should be generalized airway obstruction whose severity varies greatly over a short period of time and this should be demonstrated by pulmonary function tests with significant improvement occurring after the use of a Category I bronchodilator drug.

c. *Methods of study.* The study should consist of testing the bronchodilator drug or drugs without the sedative and in combination with a Category I sedative. The trial should be double-blind and crossover in design. The preparations should probably be given ½ hour before meals to be sure of good absorption. It is suggested that the preparation be given at the manufacturer's suggested dosage 4 times daily for 5 days, and then a crossover alternate be given for a similar period.

Two methods of evaluating the preparation should be involved:

(1) There should be a questionnaire with questions related to nervousness, insomnia, irritability, and tremor. There should also be questions related to the patient's assessment of change in his asthmatic condition. The questionnaire might best be developed in the form of a diary.

(2) Pulmonary function tests and blood gas estimations: The latter are important to determine if the sedative is producing any respiratory depressant effect. These determinations should be done at the beginning of the trial and at the end of the trial before taking the first dose and 1 hour after taking the first dose. Therefore, there should be sets of pulmonary function tests as follows:

(i) First preparation (bronchodilator alone or with a sedative): One half hour before taking the first dose of the first preparation and 1 hour after taking the first dose of the first preparation.

(ii) As above at the end of the 5 days when the last dose of the first preparation is taken.

Evidence of drug effectiveness is required from a minimum of two positive studies based on the results of two different investigators or laboratories.

All data submitted to the Food and Drug Administration must present both favorable and any unfavorable results.

(iii) Second preparation (crossover alternate with bronchodilator alone or with a sedative): After an appropriate washout period, the second preparation is given. Determinations are made ½ hour before taking the first dose of the second preparation and 1 hour after taking the first dose of the second preparation.

(iv) As above at the end of the second 5-day series when the last dose of the second preparation is taken.

(v) If possible, repeated estimations of peak expiratory flow rates should be done each day of the 5-day periods, for example, 1 hour after taking the medication.

To obtain sufficient data it will probably be necessary to test about 30 patients.

If the sedative is to be combined with a theophylline it would probably be useful to test for theophylline blood levels at intervals after an oral dose of the theophylline and after an oral dose of the theophylline plus the sedative. This is to determine whether there are any abnormalities of absorption produced. These tests need not be done on asthmatics and could probably be done on volunteers. Probably only 15 individuals need be tested.

From a safety point of view it is assumed that the bronchodilators and sedatives are all in Category I.

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Therefore, under the Federal Food, Drug, and Cosmetic Act (secs. 201, 502, 505, 701, 52 Stat. 1040–1042 as amended, 1050–1053 as amended, 1055–1056 as amended by 70 Stat. 919 and 72 Stat. 948 (21 U.S.C. 321, 352, 355, 371)) and the Administrative Procedure Act (secs. 4, 5, 10, 60 Stat. 238 and 243 as amended (5 U.S.C. 553, 554, 702, 703, 704)) and under authority delegated to him (21 CFR 5.1), (recodification published in the FEDERAL REGISTER of June 15, 1976 (41 FR 24268)) the Commissioner of Food and Drugs proposes that Subchapter D be amended by adding a new Part 341 to read as follows:

PART 341—COLD, COUGH, ALLERGY, BRONCHODILATOR AND ANTIASTHMATIC PRODUCTS FOR OVER-THE-COUNTER HUMAN USE

Subpart A—General Provisions

Sec.
341.1 Scope.
341.3 Definitions.

Subpart B—Active Ingredients

341.12 Antihistamines.
341.14 Antitussives.
341.16 Bronchodilators.
341.20 Nasal decongestants.
341.40 Permitted combinations of active ingredients.

Subpart C—Testing Procedures

341.45 Theophylline tablet dissolution testing.

Subpart D—Labeling

341.50 Labeling of cold, cough, allergy, bronchodilator and antiasthmatic products.
341.70 Products containing anticholinergics
341.72 Products containing antihistamines.
341.74 Products containing antitussives.
341.76 Products containing bronchodilators
341.78 Products containing expectorants.
341.80 Products containing nasal decongestants.
341.85 Labeling of combinations of active ingredients.
341.90 Professional labeling.

AUTHORITY: Secs. 201, 502, 505, 701, 52 Stat. 1040–42 as amended, 1050–1053 as amended, 1055–1056 as amended by 70 Stat. 919 and 72 Stat. 948 (21 U.S.C. 321, 352, 355, 371); (5 U.S.C. 553, 554, 702, 703, 704).

Subpart A—General Provisions

§ 341.1 Scope.

An over-the-counter cold, cough, allergy, bronchodilator or antiasthmatic product in a form suitable for oral, inhalant, or topical administration is generally recognized as safe and effective and is not misbranded if it meets each of the following conditions and each of the general conditions established in § 330.1 of this chapter.

§ 341.3 Definitions.

As used in this part:

(a) *Age (dosage) range.* Infant or baby (under 2 years), child (2 years to under 12 years), and adult (12 years and over).

(b) *Allergy product.* A drug product used for the relief of the symptoms of allergic rhinitis (such as hay fever).

(c) *Antiasthmatic drug.* A drug product used for the control of the symptoms of bronchial asthma.

(d) *Anticholinergic drug.* A drug used for the relief of excessive secretions of the nose and eyes, symptoms commonly associated with hay fever, allergy, rhinitis, and the "common cold" (cold).

(e) *Antihistaminic drug.* A drug used for the relief of the symptoms of mild allergic rhinitis (such as hay fever) (seasonal allergic rhinitis) and perennial allergic rhinitis.

(f) *Antitussive drug.* A drug which inhibits, controls or suppresses the act of coughing.

(g) *Asthma product.* A drug product used for the control of the symptoms of bronchial asthma.

(h) *Bronchodilator drug.* A drug used to overcome spasms that cause narrowing of the bronchial air tubes, such as in the symptomatic treatment of the wheezing and shortness of breath of asthma.

(i) *Cough product.* A drug product used to inhibit, control or suppress the act of coughing.

(j) *Expectorant drug.* A drug used to promote or facilitate the removal of secretions from the respiratory airways.

(k) *Hay fever product.* A drug product used for the relief of the symptoms of allergic rhinitis (such as hay fever).

(l) *Inhalant dosage.* The dosage range that is generally recognized as safe and effective inhaled nasally or by mouth.

(m) *Nasal decongestant drug.* A drug which reduces nasal congestion caused by acute or chronic rhinitis.

(n) *Oral dosage.* The dosage range that is generally recognized as safe and effective by mouth.

(o) *Topical dosage.* The dosage range that is generally recognized as safe and effective applied topically, such as by external rub for inhalation, as a lozenge for local application by mouth, or as drops or sprays for local application intranasally.

Subpart B—Active Ingredients

§ 341.12 Antihistamines.

The active ingredients of the product consist of the following within the dosage limit established for each ingredient:

(a) *Brompheniramine maleate.* Adult oral dosage is 4 mg every 4 to 6 hours not to exceed 24 mg in 24 hours. Children 6 to under 12 years oral dosage is 2 mg every 4 to 6 hours not to exceed 12 mg in 24 hours. Children 2 to under 6 years oral dosage is identified in § 341.90(a). For children under 2 years, there is no recommended dosage except under the advice and supervision of a physician.

(b) *Chlorpheniramine maleate.* Adult oral dosage is 4 mg every 4 to 6 hours not to exceed 24 mg in 24 hours. Children 6 to under 12 years oral dosage is 2 mg every 4 to 6 hours not to exceed 12 mg in 24 hours. Children 2 to under 6 years oral dosage is identified in § 341.90(b). For children under 2 years, there is no recommended dosage except under the advice and supervision of a physician.

(c) *Diphenhydramine hydrochloride.* Adult oral dosage is 25 to 50 mg every 4 to 6 hours not to exceed 300 mg in 24 hours. Children 6 to under 12 years oral dosage is 12.5 to 25 mg every 4 to 6 hours not to exceed 150 mg in 24 hours. Children 2 to under 6 years oral dosage is identified in § 341.90(c). For children under 2 years, there is no recommended dosage except under the advice and supervision of a physician.

(d) *Doxylamine succinate.* Adult oral dosage is 7.5 to 12.5 mg every 4 to 6 hours not to exceed 75 mg in 24 hours. Children 6 to under 12 years oral dosage is 3.75 to 6.25 mg every 4 to 6 hours not to exceed 37.5 mg in 24 hours. Children 2 to under 6 years oral dosage is identified in § 341.90(d). For children under 2 years, there is no recommended dosage except under the advice and supervision of a physician.

(e) *Methapyrilene preparations.* Adult oral dosage is 50 mg every 4 to 6 hours not to exceed 300 mg in 24 hours. Children 6 to under 12 years oral dosage is 25 mg every 4 to 6 hours not to exceed 150 mg in 24 hours. Children 2 to under 6 years oral dosage is identified in § 341.90(f). For children under 2 years, there is no recommended dosage except under the advice and supervision of a physician.

(f) *Phenindamine tartrate.* Adult oral dosage is 25 mg every 4 to 6 hours not to exceed 150 mg in 24 hours. Children 6 to under 12 years oral dosage is 12.5 mg every 4 to 6 hours not to exceed 75 mg in 24 hours. Children 2 to under 6 years oral dosage is identified in § 341.90(g). For children under 2 years, there is no recommended dosage except under the advice and supervision of a physician.

(g) *Pheniramine maleate.* Adult oral dosage is 12.5 to 25 mg every 4 to 6 hours not to exceed 150 mg in 24 hours. Children 6 to under 12 years oral dosage is 6.25 to 12.5 mg every 4 to 6 hours not to exceed 75 mg in 24 hours. Children 2 to under 6 years oral dosage is identified in § 341.90(h). For children under 2 years, there is no recommended dosage except under the advice and supervision of a physician.

(h) *Promethazine hydrochloride.* Adult oral dosage is 6.25 to 12.5 mg every 8 to 12 hours not to exceed 37.5 mg in 24 hours. Children 6 to under 12 years oral dosage is 3.125 to 6.25 mg every 8 to 12 hours not to exceed 18.75 mg in 24 hours. Children 2 to under 6 years oral dosage is identified in § 341.90(i). For children under 2 years, there is no recommended dosage except under the advice and supervision of a physician.

(i) *Pyrilamine maleate.* Adult oral dosage is 25 to 50 mg every 6 to 8 hours not to exceed 200 mg in 24 hours. Children 6 to under 12 years oral dosage is 12.5 to 25 mg every 6 to 8 hours not to exceed 100 mg in 24 hours. Children 2 to under 6 years oral dosage is identified in § 341.90(j). For children under 2 years, there is no recommended dosage except under the advice and supervision of a physician.

(j) *Thonzylamine hydrochloride.* Adult oral dosage is 50 to 100 mg every 4 to 6 hours not to exceed 600 mg in 24 hours. Children 6 to 12 years oral dosage is 25 to 50 mg every 4 to 6 hours not to exceed 300 mg in 24 hours. Children 2 to under 6 years oral dosage is identified in § 341.90(1). For children under 2 years, there is no recommended dosage except under the advice and supervision of a physician.

§ 341.14 Antitussives.

The active ingredients of the product consist of the following within the dosage limit established for each ingredient:

(a) *Codeine preparations (codeine, codeine alkaloid, codeine phosphate, codeine sulfate).* (1) Adult oral dosage is 10 to 20 mg every 4 to 6 hours not to exceed 120 mg in 24 hours. Children 6 to under 12 years oral dosage is 5 to 10 mg every 4 to 6 hours not to exceed 60 mg in 24 hours. Children 2 to under 6 years oral dosage is 2.5 to 5 mg every 4 to 6 hours not to exceed 30 mg in 24 hours. For children under 2 years, there is no recommended dosage except under the advice and supervision of a physician.

(2) Shall apply to products pursuant to the requirements identified in § 329.20(a) and § 1308.15(b) of this chapter.

(b) *Dextromethorphan, dextromethorphan hydrobromide.* Adult oral dosage is 10 to 20 mg every 4 hours or 30 mg every 6 to 8 hours not to exceed 120 mg in 24 hours. Children 6 to under 12 years oral dosage is 5 to 10 mg every 4 hours or 15 mg every 6 to 8 hours not to exceed 60 mg in 24 hours. Children 2 to under 6 years oral dosage is 2.5 to 5 mg every 4 hours or 7.5 mg every 6 to 8 hours not to exceed 30 mg in 24 hours. For children under 2 years, there is no recommended dosage except under the advice and supervision of a physician.

(c) *Diphenhydramine hydrochloride.* Adult oral dosage is 25 mg every 4 hours not to exceed 150 mg in 24 hours. Children 6 to under 12 years oral dosage is 12.5 mg every 4 hours not to exceed 75 mg in 24 hours. Children 2 to under 6 years oral dosage is identified in § 341.90(c). For children under 2 years, there is no recomended dosage except under the advice and supervision of a physician.

§ 341.16 Bronchodilators.

The active ingredients of the product consist of the following within the dosage limit established for each ingredient:

(a) *Ephedrine preparations, (ephedrine, ephedrine hydrochloride, ephedrine sulfate, racephedrine hydrochloride).* Adult oral dosage is 12.5 to 25 mg not more often than every 4 hours not to exceed 150 mg in 24 hours. Children 2 to under 12 years oral dosage is identified in § 341.90(e). For children under 2 years, there is no recommended dosage except under the advice and supervision of a physician.

(b) *Epinephrine preparations (epinephrine, epinephrine bitartrate, epi-*

nephrine hydrochloride (racemic) (inhalant)). Adults and children 4 years and above inhalation dosage is 1 to 3 inhalations of a 1 percent aqueous solution of 1-epinephrine or the equivalent in a pressurized preparation not more often than every 3 hours, except under the advice and supervision of a physician. For children under 4 years, there is no recommended dosage except under the advice and supervision of a physician.

Children and adolescents should not have unsupervised access to this inhaler. There is the possibility of abuse of this material and possible adverse effects on the heart if excessively used.

(c) *Methoxyphenamine hydrochloride.* Adult oral dosage is 100 mg every 4 to 6 hours not to exceed 600 mg in 24 hours. For children under 12 years, there is no recommended dosage except under the advice and supervision of a physician.

(d) *Theophylline preparations (aminophylline, theophylline anhydrous, theophylline calcium salicylate, theophylline sodium glycinate).* Adult oral dosage based on the anhydrous theophylline equivalent is 100 to 200 mg every 6 hours not to exceed 800 mg in 24 hours. Children 2 to under 12 years oral dosage is identified in § 341.90(k). For children under 2 years, there is no recommended dosage except under the advice and supervision of a physician.

§ 341.20 Nasal decongestants.

The active ingredients of the product consist of the following within the dosage limit established for each ingredient:

(a) *Ephedrine preparations (ephedrine, ephedrine hydrochloride, ephedrine sulfate, racephedrine hydrochloride) (topical).* Adult topical dosage is 2 to 3 drops or sprays in each nostril of a 0.5 percent aqueous solution not more frequently than every 4 hours. Children 6 to under 12 years topical dosage is 1 or 2 drops or sprays of a 0.5 percent solution not more frequently than every 4 hours. For children under 6 years, there is no recommended dosage except under the advice and supervision of a physician.

(b) *Naphazoline hydrochloride (topical).* Adult topical dosage is 1 to 2 drops or sprays of a 0.05 percent aqueous solution in each nostril not more frequently than every 6 hours. Children 6 to under 12 years topical dosage is 1 to 2 drops or sprays of a 0.025 percent aqueous solution in each nostril not more frequently than every 6 hours. For children under 6 years, there is no recommended dosage except under the advice and supervision of a physician.

(c) *Oxymetazoline hydrochloride (topical).* Adults and children 6 to under 12 years topical dosage is 2 to 3 drops or sprays of a 0.05 percent aqueous solution in each nostril 2 times daily (in the morning and evening). Children 2 to under 6 years topical dosage is 2 to 3 drops of a 0.025 percent aqueous solution in each nostril 2 times daily (in the morning and evening). Only drops should be used in children 2 to under 6 years since the spray is difficult to use in the small nostril. For children under 2 years, there is no recommended dosage except under the advice and supervision of a physician.

(d) *Phenylephrine hydrochloride (oral/topical*—(1) *As an oral nasal decongestant.* Adult oral dosage is 10 mg every 4 hours not to exceed 60 mg in 24 hours. Children 6 to under 12 years oral dosage is 5 mg every 4 hours not to exceed 30 mg in 24 hours. Children 2 to under 6 years oral dosage is 2.5 mg every 4 hours not to exceed 15 mg in 24 hours. For children under 2 years, there is no recommended dosage except under the advice and supervision of a physician.

(2) *As a topical nasal decongestant.* Adult topical dosage is 2 to 3 drops or sprays in each nostril of a 0.25 to 0.5 percent aqueous solution not more frequently than every 4 hours. Children 6 to under 12 years topical dosage is 2 to 3 drops or sprays in each nostril of a 0.25 percent aqueous solution not more frequently than every 4 hours. Children 2 to under 6 years topical dosage is 2 to 3 drops in each nostril of a 0.125 percent aqueous solution not more frequently than every 4 hours. Only drops should be used in children 2 to under 6 years since the spray is difficult to use in the small nostril. For children under 2 years, there is no recommended dosage except under the advice and supervision of a physician.

(e) *Phenylpropanolamine preparations (phenylpropanolamine bitartrate, phenylpropanolamine hydrochloride, phenylpropanolamine maleate) (oral).* Dosages are based on the phenylpropanolamine hydrochloride equivalent. Adult oral dosage is 25 mg every 4 hours or 50 mg every 8 hours not to exceed 150 mg in 24 hours. Children 6 to under 12 years oral dosage is 12.5 mg every 4 hours or 25 mg every 8 hours not to exceed 75 mg in 24 hours. Children 2 to under 6 years oral dosage is 6.25 mg every 4 hours or 12.5 mg every 8 hours not to exceed 37.5 mg in 24 hours. For children under 2 years, there is no recommended dosage except under the advice and supervision of a physician.

(f) *Propylhexedrine (inhalant).* Adults and children 6 to under 12 years inhalant dosage from an inhaler that shall deliver in each 800 ml of air 0.40 to 0.50 mg of propylhexedrine is 2 inhalations in each nostril not more frequently than every 2 hours. For children under 6 years, there is no recommended dosage except under the advice and supervision of a physician. The inhaler should retain effectiveness for a minimum of 2 to 3 months.

(g) *Pseudoephedrine preparations (pseudoephedrine hydrochloride, pseudoephedrine sulfate) (oral).* Adult oral dosage is 60 mg every 4 hours not to exceed a maximum of 360 mg in 24 hours. Children 6 to under 12 years oral dosage is 30 mg every 4 hours not to exceed 180 mg in 24 hours. Children 2 to under 6 years oral dosage is 15 mg every 4 hours not to exceed 90 mg in 24 hours. For children under 2 years, there is no recommended dosage except under the advice and supervision of a physician.

(h) *Xylometazoline hydrochloride (topical).* Adult topical dosage is 2 to 3 drops or sprays in each nostril of a 0.1 percent aqueous solution every 8 to 10 hours. Children 2 to under 12 years topical dosage is 2 to 3 drops or sprays in each nostril of a 0.05 percent aqueous solution every 8 to 10 hours. Only drops should be used in children 2 to under 6 years since the spray is difficult to use in the small nostril. For children under 2 years, there is no recommended dosage except under the advice and supervision of a physician.

§ 341.40 Permitted combinations of active ingredients.

(a) Any single antihistamine active ingredient identified in § 341.12 may be combined with any single generally recognized as safe and effective analgesic-antipyretic active ingredient: *Provided,* That the combination contains any applicable labeling identified in § 341.85(d).

(b) Any single antihistamine active ingredient identified in § 341.12 may be combined with any single oral nasal decongestant active ingredient identified in § 341.20.

(c) Any single antihistamine active ingredient identified in § 341.12 may be combined with any single oral nasal decongestant active ingredient identified in § 341.20 with any single generally recognized as safe and effective analgesic-antipyretic active ingredient: *Provided,* That the combination contains the labeling identified in § 341.85(d).

(d) Any single antihistamine active ingredient identified in § 341.12 may be combined with any single antitussive active ingredient identified in § 341.14: *Provided,* That the combination contains the labeling identified in § 341.85(a).

(e) Any single antihistamine active ingredient identified in § 341.12 may be combined with any single oral nasal decongestant active ingredient identified in § 341.20 with any single antitussive active ingredient identified in § 341.14.

(f) Any single antitussive active ingredient identified in § 341.14 may be combined with any single oral bronchodilator active ingredient identified in § 341.16: *Provided,* That the combination contains the labeling identified in § 341.85(b).

(g) Any single antitussive active ingredient identified in § 341.14 may be combined with any single generally recognized as safe and effective expectorant active ingredient.

(h) Any single antitussive active ingredient identified in § 341.14 may be combined with any single oral nasal decongestant active ingredient identified in § 341.20.

(i) Any single antitussive active ingredient identified in § 413.14 may be combined with any single generally recognized as safe and effective expectorant active ingredient with any single oral nasal decongestant active ingredient identified in § 341.20.

(j) Any single antitussive active ingredient identified in § 341.14 may be combined with any single generally recognized as safe and effective local anesthetic or local analgesic active in-

gredient: *Provided*, That the product is available only as a lozenge.

(k) Any single bronchodilator active ingredient identified in § 341.16(a) may be combined with any single bronchodilator active ingredient identified in § 341.16(d).

(l) Any single oral bronchodilator active ingredient identified in § 341.16 may be combined with any single generally recognized as safe and effective expectorant active ingredient: *Provided*, That the combination contains the labeling identified in § 341.85(c).

(m) Any single oral nasal decongestant active ingredient identified in § 341.20 may be combined with any single generally recognized as safe and effective analgesic-antipyretic active ingredient: *Provided*, That the combination contains the labeling identified in § 341.85(d).

(n) Any single oral nasal decongestant active ingredient identified in § 341.20 may be combined with any single generally recognized as safe and effective expectorant active ingredient.

(o) Any single nasal decongestant active ingredient identified in § 341.20 may be combined with any single generally recognized as safe and effective local anesthetic or local analgesic active ingredient: *Provided*, That the product is available only as a lozenge.

Subpart C—Testing Procedures

§ 341.45 Theophylline tablet dissolution testing.

All tablet product formulations containing theophylline preparation(s) identified in § 341.16(d) shall be tested according to the procedures described in the United States Pharmacopeia XIX (page 651). The tablets shall be suitable for OTC use if the quantity of theophylline dissolved within 15 minutes is not less than 50 percent of the labeled amount, based on the anhydrous theophylline, equivalent content, and the quantity of theoplylline dissolved within 30 minutes is not less than 90 percent of the labeled amount of theophylline, based on the anhydrous theophylline equivalent content, for each of the tablets tested. The resulting data shall be submitted by petition to the Food and Drug Administration for approval prior to use. The petition and the data contained therein shall be maintained in a permanent file for public review by the office of the Hearing Clerk, Food and Drug Administration, Rm. 4–65, 5600 Fishers Lane, Rockville, MD 20852.

Subpart D—Labeling

§ 341.50 Labeling of cold, cough, allergy, bronchodilator, and antiasthmatic products.

(a) *Indications.* (1) The labeling shall identify the product pursuant to the appropriate definition(s) established in § 341.3 and shall contain the applicable labeling for the active ingredient(s) as set forth in §§ 341.70, 341.72, 341.74, 341.76, 341.78, and 341.80.

(2) In addition, labeling may also contain the following indication(s): *Provided*, That such phrase(s) is combined and contiguous with the indications required as set forth in § 341.50(a)(1):

(i) "as may be associated with the common cold (cold)."

(ii) "as may occur in the common cold (cold)."

(b) *Directions for use.* The labeling of the product contains the recommended dosage and appropriate directions identified under §§ 341.12, 341.14, 341.16, or 341.20 under the heading "Directions," per time interval, e.g., every 4 hours, or other time period, e.g., 3 times daily, broken down by age groups, if appropriate, followed by "or as directed by a physician."

(c) *Warnings.* The labeling of the product contains the appropriate warning(s) under §§ 341.70, 341.72, 341.74, 341.76, 341.78, or 341.80 and, if applicable, the following general warning under the heading "Warning," which may be combined to eliminate duplicative words or phrases so the resulting warning is clear and understandable. For products containing an alcoholic content greater than 10 percent (weight/weight) "Do not give this product to children under 6 years except under the advice and supervision of a physician".

(d) *Drug interaction precautions.* The labeling of the product, where appropriate under § 341.76 or § 341.80, contains drug interaction precautions, under the heading "Drug Interaction Precautions".

§ 341.70 Products containing anticholinergics.

(a) *Indications.* The labeling of the product shall contain any of the following indications, under the heading "Indications":

(1) "For temporary relief of watery nasal discharge and watering eyes as may occur in certain allergic conditions and infections of the upper respiratory tract".

(2) "Temporarily suppresses watery nasal discharge".

(3) "Temporary relief from excessive nasal secretions".

(4) "Temporary relief from running nose".

(5) "Temporarily suppresses watering of eyes".

(b) *Warnings.* The labeling of the product contains the following warnings, under the heading "Warning":

(1) "Do not exceed recommended dosage except under the advice and supervision of a physician".

(2) "Do not continue to take this product if constipation, excessive dryness of the mouth, insomnia, excitement, confusion, rapid pulse, or blurring of vision occur".

(3) *"Caution:* Do not take this product if you have asthma, glaucoma or have difficulty in urination due to enlargement of the prostate gland except under the advice and supervision of a physician".

(4) "Do not give this product to children under 12 years except under the advice and supervision of a physician".

§ 341.72 Products containing antihistamines.

(a) *Indications.* The labeling of the product shall contain any of the following indications, under the heading "Indications":

(1) "Alleviates, decreases, or for temporary relief of, running nose, sneezing, itching of the nose or throat and itchy and watery eyes as may occur in allergic rhinitis (such as hay fever)".

(2) "Alleviates, decreases, or for temporary relief of, running nose as may occur in allergic rhinitis (such as hay fever)".

(3) "Alleviates, decreases, or for temporary relief of, sneezing as may occur in allergic rhinitis (such as hay fever)".

(4) "Alleviates, decreases, or for temporary relief of, itching of the nose or throat as may occur in allergic rhinitis (such as hay fever)".

(5) "Alleviates, decreases, or for temporary relief of, itchy and watery eyes as may occur in allergic rhinitis (such as hay fever)".

(6) "Dries running nose as may occur in allergic rhinitis (such as hay fever)".

(b) *Warnings.* The labeling of the product contains the following warnings, under the heading "Warnings":

(1) "May cause excitability especially in children".

(2) "Do not take this product if you have asthma, glaucoma or difficulty in urination due to enlargement of the prostrate gland except under the advice and supervision of a physician".

(3) *"Caution:* Avoid driving a motor vehicle or operating heavy machinery".

(4) *"Caution:* Avoid alcoholic beverages while taking this product".

(5) "Do not give this product to children under 6 years except under the advice and supervision of a physician".

(6) For products containing the active ingredients identified in paragraphs (a), (b), (f), (i), and (j) of § 341.12: "May cause drowsiness".

(7) For products containing the active ingredients identified in paragraphs (c), (d), (e), (g), and (h) of § 341.12: "May cause marked drowsiness".

(8) For products containing an active ingredient identified in § 341.12(f): *"Caution:* May cause nervousness and insomnia in some individuals".

§ 341.74 Products containing antitussives.

(a) *Indications.* The labeling of the product may contain any of the following indications, under the heading "Indications": (1) "Cough suppressant which temporarily reduces the impulse to cough".

(2) "For the temporary relief of cough due to minor throat and bronchial irritation as may occur with the common cold (cold) or with inhaled irritants".

(3) "Temporarily quiets coughing by its antitussive action".

(4) "Temporarily helps you cough less".

(5) "Temporarily helps to quiet the cough reflex that causes coughing".

(6) For products containing an ingredient identified in § 341.14(a): "Calms the cough control center and relieves coughing".

(7) For products containing an ingredient identified in § 341.14 (b) and (c):

(i) "Calms the cough control center and relieves coughing".

(ii) "Non-narcotic cough suppressant for the temporary control of coughs".

(iii) "Calms cough impulses without narcotics".

(b) *Warnings.* The labeling of the product contains the following warnings, under the heading "Warnings": (1) "Do not give this product to children under 2 years except under the advice and supervision of a physician".

(2) "Do not take this product for persistent or chronic cough such as occurs with smoking, asthma, or emphysema, or where cough is accompanied by excessive secretions except under the advice and supervision of a physician".

(3) *"Caution:* A persistent cough may be a sign of a serious condition. If cough persists for more than 1 week, tends to recur or is accompanied by high fever, rash or persistent headache, consult a physician".

(4) For products containing an ingredient identified in § 341.14(a):

(i) "May cause or aggravate constipation".

(ii) "Do not give this product to children taking other drugs except under the advice and supervision of a physician".

(iii) "Do not take this product if you have a chronic pulmonary disease or shortness of breath except under the advice and supervision of a physician".

(5) For products containing an ingredient identified in § 341.14(c): (i) May cause marked drowsiness".

(ii) "May cause excitability especially in children".

(iii) "Do not take this product if you have glaucoma or have difficulty in urination due to enlargement of the prostate gland except under the advice and supervision of a physician".

(iv) "Caution: Avoid driving a motor vehicle or operating heavy machinery".

(v) "Do not give this product to children under 6 years except under the advice and supervision of a physician".

§ 341.76 Products containing bronchodilators.

(a) *Indications.* (1) The labeling of a product to be taken by inhalation may contain under the heading "Indications" the time to onset of action expressed in minutes.

(2) The labeling of the product shall contain any of the following indications, under the heading "Indications":

(i) "For temporary relief of bronchial asthma".

(ii) "For symptomatic control of bronchial asthma".

(iii) "Provides temporary relief from acute symptoms of bronchial asthma".

(iv) "Relaxes tense bronchial muscles to ease breathing for asthma patients".

(v) "For temporary relief of wheezing (attacks and distress) of bronchial asthma".

(b) *Warnings.* The labeling of the product contains the following warning, under the heading "Warnings": (1) "Caution: Do not take this product unless a diagnosis of asthma has been made by a physician".

(2) For products containing an ingredient identified in § 341.16 (a) and (c):

(i) *"Caution:* Do not continue to take this product but seek medical assistance immediately if symptoms are not relieved within 1 hour or become worse".

(ii) "Nervousness, tremor, sleeplessness, nausea and loss of appetite may occur".

(iii) "Do not take this product if you have heart disease, high blood pressure, thyroid disease, diabetes or difficulty in urination due to enlargement of the prostate gland".

(iv) *Drug interaction precaution.* "Do not take this product if you are presently taking a prescription antihypertensive or antidepressant drug containing a monoamine oxidase inhibitor".

(v) "Do not give this product to children under 12 years except under the advice and supervision of a physician".

(3) For products containing an ingredient identified in § 341.16(b):

(i) "Do not take this product at higher than recommended doses except under the advice and supervision of a physician for it may cause nervousness and rapid heart beat".

(ii) *"Caution:* Do not continue to take this product but seek medical assistance immediately if symptoms are not relieved within 20 minutes or become worse".

(iii) "Do not take this product if you have heart disease or high blood pressure except under the advice and supervision of a physician".

(iv) *Drug interaction precaution.* "Do not take this product of you are presently taking a prescription antihypertensive or antidepressant drug containing a monamine oxidase inhibitor".

(v) "Keep this product out of reach of children and adolescents because unsupervised access may cause abuse or possible adverse effects on the heart if excessively used".

(vi) "Do not give this product to children under 4 years except under the advice and supervision of a physician".

(4) For products containing an ingredient identified in § 341.16(d):

(i) "Do not exceed recommended dosage except under the advice and supervision of a physician".

(ii) "Do not take this product if nausea, vomiting or restlessness occurs".

(iii) *"Caution:* Do not continue to take this product but seek medical assistance immediately if symptoms are not relieved within 1 hour or become worse".

(iv) "Do not take this product if you are presently taking a drug or suppository containing any form of theophylline except under the advice and supervision of a physician".

(v) "Do not give this product to children under 12 years except under the advice and supervision of a physician. Excessive use may cause toxic effects and even death in children".

§ 341.78 Products containing expectorants.

(a) *Indication.* The labeling of the product may contain any of the following indications, under the heading "Indications":

(1) "Helps loosen phlegm (sputum)".

(2) "Helps rid the passageways of bothersome mucus".

(3) "Expectorant action to help loosen phlegm (sputum) and bronchial secretions".

(4) "Helps drainage of bronchial tubes by thinning the mucus".

(5) "Relieves irritated membranes in the respiratory passageways by preventing dryness through increased mucus flow".

(b) *Warnings.* The labeling of the product contains the following warnings, under the heading, "Warnings":

(1) "Do not give this product to children under 2 years except under the advice and supervision of a physician".

(2) "Do not take this product for persistent or chronic cough such as occurs with smoking, asthma, or emphysema, or where cough is accompanied by excessive secretions except under the advice and supervision of a physician".

(3) *"Caution:* A persistent cough may be a sign of a serious condition. If cough persists for more than 1 week, tends to recur or is accompanied by high fever, rash or persistent headache, consult a physician".

§ 341.80 Products containing nasal decongestants.

(a) *Indications.* The labeling of the product shall contain any of the following indications, under the heading "Indications":

(1) "For temporary relief of nasal congestion due to the common cold (cold)".

(2) "For temporary relief of nasal congestion due to hay fever or other upper respiratory allergies".

(3) "For temporary relief of nasal congestion associated with sinusitus".

(4) "For the temporary relief of stuffy nose (stopped up nose, nasal stuffiness, clogged up nose)".

(5) "Reduces swelling of nasal passages; shrinks swollen membranes".

(6) "Decongest nasal passages".

(7) "Temporarily restores freer breathing through the nose".

(8) "Helps clear nasal passages".

(9) "Helps decongest sinus openings, sinus passages".

(10) "Promotes nasal and/or sinus drainage".

(11) For products with claims for duration of effect: Statements as to duration of effect must be substantiated and accompanied by a specific time period expressed in minutes or hours, as appropriate.

(12) For products to be used as topical nasal decongestants with claims for rapid onset of action: Statements relating to time to onset of action, such as, "fast" or "quick", must be accompanied by a specific time period expressed in minutes.

(13) For products to be used as topical nasal decongestants which can demonstrate a cooling sensation:

(i) "Provides cooling sensation".

(ii) "Cooling".

(iii) "Cools nasal passages".

(b) *Warnings.* The label of the product contains the following warnings, under the heading "Warnings".

(1) For products containing topical nasal decongestants:

(i) "Do not exceed recommended dosage because symptoms may occur such as burning, stinging, sneezing, or increase of nasal discharge.

(ii) "Do not use this product for more than 3 days. If symptoms persist, consult a physician".

(iii) "The use of this dispenser by more than one person may spread infection".

(2) For products used as oral nasal decongestants:

(i) "Do not exceed recommended dosage because at higher doses nervousness, dizziness, or sleeplessness may occur".

(ii) "If symptoms do not improve within 7 days or are accompanied by high fever, consult a physician before continuing use".

(iii) "Do not take this preparation if you have high blood pressure, heart disease, diabetes, or thyroid disease except under the advice and supervision of a physician".

(iv) *"Drug interaction precaution:* Do not take this product if you are presently taking a prescription antihypertensive or antidepressant drug containing a monoamine oxidase inhibitor except under the advice and supervision of a physician".

(3) For products used as inhalant nasal decongestants:

(i) "This inhaler should be warmed in the hand before use to increase effectiveness".

(ii) "Do not give this product to children under 6 years except under the advice and supervision of a physician".

(iii) "Children should not have unsupervised access to this inhaler".

(iv) *"Caution:* Not for use by mouth".

(4) For products containing the active ingredient identified in § 341.20(a) at a concentration of 0.5 percent: "Do not give this product to children under 6 years except under the advice and supervision of a physician".

(5) For products containing the active ingredient identified in § 341.20(b) at a concentration of 0.025 percent: "Do not give this product to children under 6 years except under the advice and supervision of a physician".

(6) For products containing the active ingredient identified in § 341.20(b) at a concentration of 0.05 percent: "For adult use only. Do not give this product to children under 6 years since it may cause sedation if swallowed".

(7) For products containing the active ingredient identified in § 341.20(d) (2) at a concentration of 0.125 percent: "Do not give this product to children under 2 years except under the advice and supervision of a physician".

(8) For products containing the active ingredient identified in § 341.20(d) (2) at a concentration of 0.25 percent: "Do not give this product to children under 6 years except under the advice and supervision of a physician".

(9) For products containing the active ingredient identified in § 341.20(d) (2) at a concentration of 0.5 percent: "For adult use only. Do not give this product to children under 12 years except under the advice and supervision of a physician".

(10) For products containing the active ingredient identified in § 341.20(h) at a concentration of 0.05 percent: "Do not give this product to children under 2 years except under the advice and supervision of a physician".

(11) For products containing the active ingredient identified in § 341.20(h) at a concentration of 0.1 percent: "For adult use only. Do not give this product to children under 12 years except under the advice and supervision of a physician".

§ 341.85 Labeling of combinations of active ingredients.

(a) *Antihistamine combined with an antitussive.* A combination identified in § 341.40(d) shall contain the following warning under the heading "Warning": "Caution: May cause marked drowsiness". The Food and Drug Administration will grant an exemption to the labeling term "marked", which may be removed from the warning statement upon petition if adequate data are submitted to demonstrate that the combination product does not cause a significant increase in drowsiness as compared with each active ingredient when tested alone. The petition and the data contained therein shall be maintained in a permanent file for public review by the office of the Hearing Clerk, Food and Drug Administration, Rm. 4–65, 5600 Fishers Lane, Rockville, MD 20852.

(b) *Antitussive combined with a bronchodilator.* A combination identified in § 341.40(f) shall contain the following warning, under the heading "Warning": "This product should be used only for cough associated with asthma".

(c) *Bronchodilator combined with an expectorant.* A combination identified in § 341.40(1) shall contain the following warning, under the heading "Warning": "This product should be used only for cough associated with asthma".

(d) *Aspirin (acetylsalicylic acid) containing combinations.* Any combination identified in § 341.40 (a), (c), or (m) containing aspirin (acetylsalicylic acid) shall contain the following warning, under the heading "Warning": "This product contains aspirin and should not be taken by individuals who are sensitive to aspirin".

§ 341.90 Professional labeling.

The labeling of the product provided to health professionals (but not to the general public) may contain the following additional dosage information for products containing the active ingredients identified below:

(a) For products containing brompheniramine maleate: Children 2 to under 6 years oral dosage is 1 mg every 4 to 6 hours not to exceed 6 mg in 24 hours.

(b) For products containing chlorpheniramine maleate: Children 2 to under 6 years oral dosage is 1 mg every 4 to 6 hours not to exceed 6 mg in 24 hours.

(c) For products containing diphenhydramine hydrochloride:

(1) *For use as an antihistamine:* Children 2 to under 6 years oral dosage is 6.25 mg every 4 to 6 hours not to exceed 37.5 mg in 24 hours.

(2) *For use as an antitussive:* Children 2 to under 6 years oral dosage is 6.25 mg every 4 hours not to exceed 37.5 mg in 24 hours.

(d) *For products containing doxylamine succinate:* Children 2 to under 6 years oral dosage is 1.9 to 3.125 mg every 4 to 6 hours not to exceed 18.75 mg in 24 hours.

(e) *For products containing ephedrine preparations for use as a bronchodilator (ephedrine, ephedrine hydrochloride, ephedrine sulfate, racephedrine hydrochloride):* Children 6 to under 12 years oral dosage is 6.25 to 12.5 mg not more often than every 4 hours not to exceed 75 mg in 24 hours. Children 2 to under 6 years oral dosage is 0.3 to 0.5 mg/kg of body weight not more often than every 4 hours not to exceed 2 mg/kg of body weight in 24 hours.

(f) *For products containing methapyrilene preparations (methapyrilene fumarate, methapyrilene hydrochloride):* Children 2 to under 6 years oral dosage is 12.5 mg every 4 to 6 hours not to exceed 75 mg in 24 hours.

(g) *For products containing phenindamine tartrate:* Children 2 to under 6 years oral dosage is 6.25 mg every 4 to 6 hours not to exceed 37.5 mg in 24 hours.

(h) *For products containing pheniramine maleate:* Children 2 to under 6 years oral dosage is 3.125 to 6.25 mg every 4 to 6 hours not to exceed 37.5 mg in 24 hours.

(i) *For products containing promethazine hydrochloride:* Children 2 to under 6 years oral dosage is 1.56 to 3.125 mg every 8 to 12 hours not to exceed 9.375 mg in 24 hours.

(j) *For products containing pyrilamine maleate:* Children 2 to under 6 years oral dosage is 6.25 to 12.5 mg every 6 to 8 hours not to exceed 50 mg in 24 hours.

(k) *For products containing theophylline preparations (aminophylline, theophylline anhydrous, theophylline calcium salicylate, theophylline sodium glycinate):* Children 2 to under 12 years oral dosage based on the anhydrous theophylline equivalent is 3.33 mg/kg of body weight 3 times daily every 8 hours not to exceed 10 mg/kg in 24 hours.

(l) For products containing thonzylamine hydrochloride: Children 2 to under 6 years oral dosage is 12.5 to 25 mg every 4 to 6 hours not to exceed 150 mg in 24 hours.

Interested persons are invited to submit their comments in writing (preferably in quintuplicate and identified with the Hearing Clerk docket number found in brackets in the heading of this document) regarding this proposal on or before December 8, 1976. Such comments should be addressed to the office of the Hearing Clerk, Food and Drug Administration, Rm. 4–65, 5600 Fishers Lane, Rockville, MD 20852, and may be accompanied by a memorandum or brief in support thereof. Additional comments replying to any comments so filed may also be submitted on or before January 7, 1977. Received comments may be seen in the above office during working hours, Monday through Friday.

Dated: July 30, 1976.

SHERWIN GARDNER,
Acting Commissioner of Food and Drugs.

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